Cardiofacio-cutaneous syndrome: Classical presentation of a rare genodermatoses

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Access this article online

Website: www.idoj.in

DOI: 10.4103/2229-5178.190508

Quick Response Code:

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ABSTRACT

Cardiofacio-cutaneous syndrome is a rare genodermatoses with multiple congenital anomalies (MCA) and mental retardation. Although various mutations have been described, the diagnosis can be made clinically based on constellation of symptoms. Herein, we report a classical case with typical craniofacial features and atrial septal defect.

Key words: Cardiofacio-cutaneous syndrome, genodermatoses, RASopathy

INTRODUCTION

Cardiofacio-cutaneous (CFC) syndrome (OMIM: 115150) is a rare, sporadic, heterogeneous disorder first described by Reynolds *et al*. in 1986. CFC syndrome is characterized by multiple congenital anomalies consisting of peculiar craniofacial dysmorphism, congenital heart defects, ectodermal anomalies, and psychomotor retardation.[1] Various mutations have been described mainly, BRAF, MEK1, MEK2, and KRAS. Till now, approximately 100 cases are reported in the literature, with only a few reports from India.

CASE REPORT

A 4-year-old child born out of a nonconsanguineous marriage was brought by his parents for generalized dryness of skin since birth. The child was born through normal vaginal delivery but suffered from delayed developmental milestones and retarded growth. There were no other systemic complaints.

Dermatological examination revealed the presence of follicular keratotic lesions over trunk and bilateral extremities with dry scaly erythematous plaques over face and extremities. Multiple hyperkeratotic erythematous plaques of size varying from 1 to 3 cm with partially adherent thick yellowish whitish scaling over extensor surfaces of both legs were also present [Figure 1]. He also had hyperlinearity of palms and soles. The child was found to have coarse scalp hair with sparseness of eyebrows and eyelashes, frontal bossing, bitemporal narrowing, broad base nose, and prominent philtrum [Figure 2]. Nails were normal.

Other systemic examination revealed hypertelorism, strabismus, and hypotonia of the abdomen. The child was found to have atrial septal defect on 2-D echocardiography [Figure 3]. Psychiatric evaluation revealed mild mental retardation by sanguine form board (SFB) test. Rest of the systemic examinations were found to be within normal limits. No other siblings and family members were affected. These constellations of findings were consistent with the diagnosis of CFC syndrome.

Molecular genetic analysis for mutation could not be done in our patient because of financial constraints and unavailability of analysis in our institute.

Cite this article as: Prajapat M, Kothiwala SK, Sharma M, Kuldeep CM. Cardiofacio-cutaneous syndrome: Classical presentation of a rare genodermatoses. Indian Dermatol Online J 2016;7:396-8.

DISCUSSION

Germline mutations in a number of genes coding transducers and modulatory proteins participating in the RAS-MAP kinase-signaling pathway have been causally linked to Noonan syndrome (NS) and a group of clinically related disorders, the so-called neuro-CFC syndromes or RASopathies.[2] CFC syndrome is a rare RASopathy characterized by distinctive craniofacial features, cardiac anomalies, neurocognitive impairment, ectodermal abnormalities, and failure to thrive. CFC syndrome is caused by heterogeneous, heterozygous activating germline mutations in BRAF, MEK1, MEK2, and KRAS genes.[3]

The first three cases of CFC syndrome were reported by Blumberg in 1979 but the term itself was coined by Reynolds in the year 1986.[4] The typical craniofacial features include relative macrocephaly; bitemporal narrowing; hypoplastic supraorbital ridges; hypertelorism; telecanthus; down slanting palpebral fissures; epicanthal folds; short nose with depressed bridge and anteverted nares; high arched palate; low set, posteriorly rotated ears; short, webbed neck; prominent philtrum; and submucous cleft palate.

Dermatological features consist of severe atopic dermatitis, ichthyosis, multiple palmar and plantar creases, hyperkeratosis of hands and feet, keratosis pilaris, café-au-lait macules, melanocytic naevi, and hemangiomas.[5] Failure to thrive can occur in infancy due to gastroesophageal reflux and the tendency to vomit and constipation.[6] However, no such abnormalites were seen in our patient.

Most common cardiac anomalies include pulmonic stenosis (45%), septal defects (23%), patent ductus arteriosus, tetralogy of fallot, and cardiomyopathy.[7] Our patient had atrial septal defect.

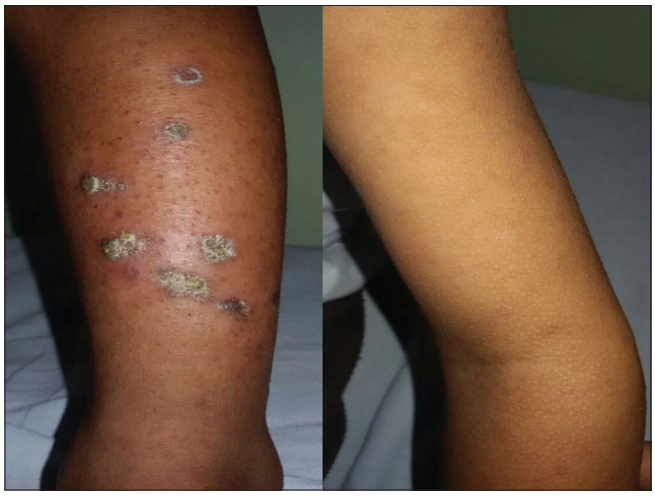

Figure 1: Left arm (right) showing multiple follicular keratotic lesions and left leg (left) showing hyperkeratotic lesions

Other rare manifestations include hearing loss, nystagmus, short stature, hepato-splenomegaly, seizures, hydrocephalus, cortical atrophy, frontal lobe hypoplasia, brainstem atrophy, and acute lymphoblastic leukemia.

The clinical diagnosis is based on the CFC index and Grebe and Clericuzio criteria (2000),[6] which include:

1. Macrocephaly
2. Ophthalmological abnormalities
3. Neurological abnormalities/developmental delay
4. History of polyhydramnios
5. Hyperkeratotic skin lesions
6. Gastrointestinal dysfunction
7. Cardiac defect
8. Sparse/curly hair
9. Characteristic facial features
10. Growth retardation

Out of the 10 clinical features, seven have to be present for the diagnosis of CFC syndrome. In our case seven features were present, that is, growth retardation, macrocephaly, ophthalmological abnormalities, developmental delay, hyperkeratotic skin lesions, cardiac defect (ASD), and

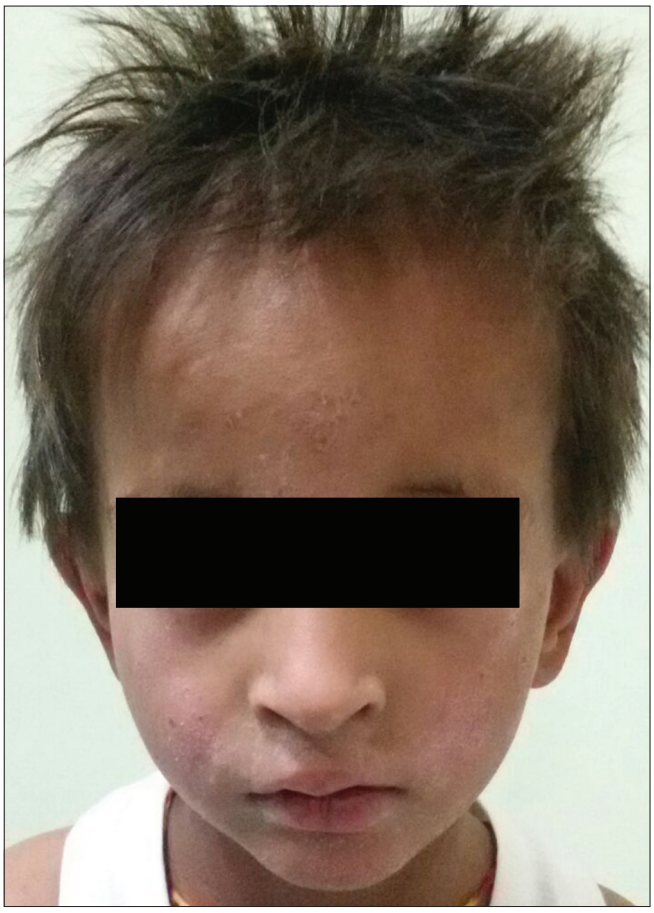

Figure 2: Typical cranio-facial features including frontal bossing, bitemporal narrowing, prominent philtrum, broad base nose, and dry scaly erythematous plaques

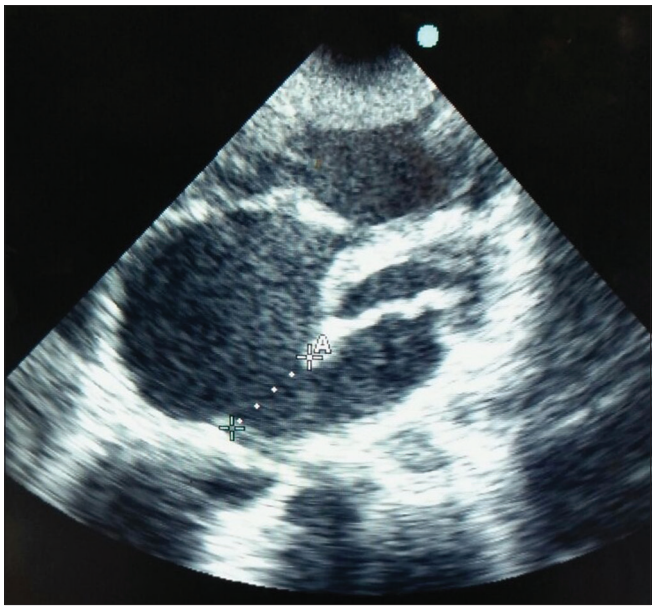

Figure 3: —Two-dimensional echocardiography showing atrial septal defects

characteristic facial features as shown in Figures 1 and 2. In NS, bleeding diasthesis; skeletal deformity, joint laxity; and lymphedema, whereas in Costello syndrome unusually flexible joints; and loose folds of extra skin, especially on the hands and feet are differenting features from CFC syndrome.

A multidisciplinary approach is usually required with emphasis on cardiac and neurological manifestations in cases of CFC syndrome. Our purpose was to highlight the various cutaneous and extracutaneous manifestations of this syndrome because of the rarity of this condition in Indian settings. We suggest that a complete workup of patients with CFC syndrome should be done for better counseling and management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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