International Journal Of Scientific And University Research Publication

ISSN No 122/350

Listed & Index with
ISSN Directory. Paris

Multi-Subject Journal

Volum : (8) | Issue : (10) |

INTERNATIONAL JOURNAL OF SCIENTIFIC AND UNIVERSITY RESEARCH PUBLICATION

Research Paper

CASE REPORT - ORAL LICHEN PLANUS IN A TEENAGER WITH CARDIOFACIOCUTANEOUS SYNDROME

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ABSTRACT **Cardiofaciocutaneous syndrome (CFCS) is an extremely rare genetic disorder that belongs to the group of syndromes known as RAS opathies. The craniofacial and ectodermal manifestations of this syndrome are distinctive and play an important role in the diagnosis of this entity. Nevertheless, there is no scientific evidence to date of the presence of CFCS-related lesions in the oral mucosa. The present study is the first to report the presence of oral lichen planus (OLP) in a patient with CFCS. This finding should be taken into account in the assessment and diagnosis of CFCS in order to establish whether it is an un-related lesion or is associated with the syndrome.**

KEYWORDS :Cardiofaciocutaneous syndrome, RAS genes, RAS proteins, RASopathies,

INTRODUCTION

Cardiofaciocutaneous syndrome (CFCS) is a genetically heterogeneous clinical entity that is inherited in a dominant autosomal manner. It belongs to a group of syndromes known as RASopathies, genetic syndromes caused by germline mutations in genes that encode components or regulators of the Ras/mitogen-activated protein kinase (MAPK) pathway (1, 2). Most cases of CFCS involve mutations in BRAF, MAP2K1, MAP2K2 and KRAS. Prevalence of CFCS is low. It affects multiple organs and systems and is characterized by the presence of craniofacial and cutaneous abnormalities. Clinical manifestations include distinctive facial dysmorphia, cardiac defects, and cutaneous abnormalities (5-7). We herein present a case of CFCS in an adolescent patient presenting lichen planus in the oral mucosa. The aim of the present work was to highlight the general typical features of CFCS, and to describe what is to our knowledge, the first case of oral lichen planus in a patient with this syndrome reported in the literature to date.

2. Case Report

A 12-year-old female patient presented for consultation at the Oral Medicine Department of the School of Dentistry, University of Buenos Aires, with a history of CFCS and reporting the presence of lesions in her oral mucosa. Diagnosis of CFCS was established based on the typical clinical features of the syndrome, and genetic tests conducted by the Genetics Service of the Garrahan Hospital of the City of Buenos Aires, Argentina.

Sequence analysis of genes PTPN11 exons 2, 3, 4, 7, 8, 12 and 13 (reference sequence NM_002834.3), SOS1 exons 6 and 10 (reference sequence NM_005633.3), RAF1 exons 7, 14 and 17 (reference sequence NM_002834.3), and BRAF exons 6, 12 and 15 (reference sequence NM_004333.4) in peripheral blood DNA showed the presence of variant c.1467>C (p.Leu489Phe) in exon 14 of gene RAF1 in heterozygous condition. The studied exons and flanking regions included the regions with the highest frequency of mutations. The detected variant has not been described previously. In silico prediction analyses indicated a potential deleterious effect of the detected variant on RAF1 function. Because the patient's mother also showed clinical features of the syndrome, the corresponding genetic sequencing was carried out, and showed the presence of variant c.1467>C (p.Leu489Phe) in exon 14 of gene RAF1 in heterozygous condition. The patient was the first offspring of a nonconsanguineous couple, and perinatal history and delivery were uneventful. The presence of typical cutaneous anomalies of the syndrome were diagnosed at the age of 3 years, and oral mucosa lesions were detected at the age of 10 years by her dentist, who referred her to our Service. Physical examination revealed dysmorphic facial features, sparse dry brittle hair, scant eyebrows, rough dry skin on the outer surface of her thighs (keratosis pilaris), tall forehead, bitemporal constriction, hypertelorism, and low-set ears. White patches and fissures were observed at both commissures of the lips (Figures 1 and 2).

Examination of the oral cavity revealed the presence of white patches, plaques and verrucous lesions in the anterior third of the cheek mucosa on both sides. Red atrophic erythematous patches, alternating with white plaques, were observed in the attached and unattached gingiva of both jaws. A keratotic white plaque and the presence of a verrucous area were observed in the middle third of the dorsal aspect of the tongue. Ogival palate and marked tooth crowding were also observed (Figures 3, 4, 5).

Based on the oral lesions, presumptive diagnosis of keratotic lichen planus was established. In order to reach definitive diagnosis, a biopsy of the cheek mucosa was taken and the following diagnostic methods were indicated: routine histopathological studies (hematoxylin-eosin and PAS staining), and direct immunofluorescence. Results of the histopathological and immunohistochemical study were consistent with oral lichen planus.

Given the presence of lesions at both commissures of the lips and on the dorsal surface of the tongue associated with Candida infection, said lesions were swabbed and sent for mycological and bacteriological examination, identification of the isolated species,

and antibacterial and antifungal susceptibility tests, in order to rule out superadded infection and to orient treatment. The isolated microorganism was Candida albicans, and administration of an antifungal drug was indicated in order to eradicate the infection.

Remission of red atrophic erythematous patches, as well as marked improvement of the verrucous areas were observed at the subsequent follow-up visits after administration of antifungal treatment for Candidiasis and of local corticoids for OLP. Only some areas of white plaques and the presence of white reticular lesions of OLP were observed.

3. **Discussion**

Within the ectodermal anomalies, follicular hyperkeratosis in the arms, legs, and face are the most frequent cutaneous abnormalities in people with CFC syndrome (8). However, although both tissues derive from the same embryonic layer, no oral mucosa anomalies have been reported to date.

Oral lichen planus (OLP) is a chronic inflammatory disease of immune nature and of unknown etiology usually presenting in middle age, and that can affect the skin, oral and genital mucosa, scalp, and nails. It has diverse clinical presentations, the most frequent being the variant observed in our patient: hyperkeratotic lichen (9). The prevalence of cutaneous lichen planus in the adult population worldwide ranges from 0.2% to 1%, whereas OLP is more frequent and has been reported to affect 1 to 4% of the population (9, 10). Overall, it affects women more often than men in a ratio of 1.5:1, and most cases develop between the age of 30 and 60 years (11, 12). In this regard, our patient was female and lichen planus occurred in the oral mucosa, both frequent observations and both in line with studies published in the literature. However, in contrast with reported findings that OLP is rare in children, with 5 to 10% of cases occurring in this age group (10, 13), the patient reported here was only 12 years old.

Although CFCS is an extremely rare genetic disorder, it must be suspected in individuals presenting the phenotypical features described above. Craniofacial and ectodermal manifestations of this syndrome are distinct and play an important role in the diagnosis of this entity. Nevertheless, there is no scientific evidence to date of the presence of lesions in the oral mucosa associated with CFCS. In this regard, it would be important to perform thorough inspection of the oral mucosa of CFCS patients to record the presence or absence of stomatological lesions, in order to determine whether these lesions are another manifestation of CFCS. In addition, it is important to point out that OLP undergoes malignant transformation in 1 to 2% of cases, so that early diagnosis is of great clinical significance in terms of prognosis and patient follow-up (14, 15).

CONCLUSION

The present study is the first to report the presence of OLP in a patient with CFCS. This finding should be taken into account when evaluating and diagnosing CFCS, with the aim to establish whether it is an occasional manifestation or whether it is associated with the syndrome.

- **Conflict of interest**

The authors declare no conflicts of interest.

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