Oral-Facial-Digital Syndrome Type 1: A Case Report and Review

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INTRODUCTION

Oral-facial-digital syndrome (OFDS) is a heterogeneous group of abnormalities of the oral cavity, face, and digits. Thus far, at least 16 subtypes have been reported depending on mode of inheritance and other abnormality of the kidneys, limbs, brain, and other organs (Table 1). Oral-facial-digital syndrome type 1 (OFD1), which is the most frequent subtype, is transmitted in an X-linked dominant mode of inheritance, with lethality in males. However, more than 70% of cases of OFD1 are sporadic. It is characterized by congenital milia and hypotrichosis, not present in other subtypes.

CASE REPORT

An 11-month-old female presented with multiple milia on her face and auricle that had been present since birth (Fig. 1A, B). Partial hypotrichosis of temporal area was also noted. Histopathologic examination on a facial skin lesion revealed a deep-seated cyst containing lamellated keratin lined by squamous epithelium with a granular layer, consistent with milium (Fig. 2). She also had congenital anomalies, including incomplete cleft palate, bifid tongue, short frenulum, anomalous deformities of both toes, and clino-brachy-syndactyly of the hands (Fig. 1D-F). We received the parent’s consent form about publishing all photographic materials. Her karyotype was normal (46, XX). Chromosomal microarray and diagnostic exome sequencing were performed and OFDI gene mutation was not found. She had no familial history of any abnormality suggestive of genetic disorder. In addition, no abnormalities were found on ophthalmic examination or abdominal and brain ultrasonography. Based on these findings, a clinical diagnosis of OFD1 was made. Her facial lesions were treated with CO2 laser and manual extraction, and the lesions have not recurred for 2 years after treatment. She is scheduled for surgery in plastic surgery department for intraoral and digital lesions.

DISCUSSION

First described by Papillon-Léage in 1954, OFDS has been
Table 1. Sixteen subtypes of oral-facial-digital syndrome (OFDS)

| Phenotype | Inheritance | Location | Gene/locus | Characteristic clinical finding |
|-----------|-------------|----------|------------|-------------------------------|
| OFDS I    | X-linked dominant | Xp22.2   | OFD1, SGBS2, JBTS10, RP23 | Milia, hypotrichosis, polycystic kidney disease |
| OFDS II   | Autosomal recessive | Not Mapped | OFD2 | Thick hair, median Y-shaped metacarpal |
| OFDS III  | Autosomal recessive | Not Mapped | OFD3 | End stage renal failure I-II decade of life |
| OFDS IV   | Autosomal recessive | 10q24.1 | TCTN3, TECT3, C10orf61, OFD4, JBTS18 | Renal cyst |
| OFDS V    | Autosomal recessive | 1q32.1 | DDX59, OFD5 | Polycystic kidney disease |
| OFDS VI   | Autosomal recessive | 5p13.2 | CPLANE1, C5orf42, JBTS17, OFD6 | Broad hallux, median Y-shaped metacarpal |
| OFDS VII  | X-linked dominant | Not Mapped | OFD7 | Tibia and radius hypoplasia |
| OFDS VIII | X-linked recessive | Chromosome X | OFD8 | Bifid toes, microphthalmia, coloboma |
| OFDS IX   | Autosomal recessive | Not Mapped | OFD9 | Bilateral short radius, fibular agenesis |
| OFDS X    | Autosomal dominant | Not Mapped | OFD10 | Odontoid hypoplasia, deafness |
| OFDS XI   | Isolated cases | Not Mapped | OFD11 | C2CD3, OFD14 |
| OFDS XV   | Autosomal recessive | 11q13.4 | KIAA0753, OFIP, OFD15 | |
| OFDS XVI  | Autosomal recessive | 17p13.1 | TMEM107, MKS13, JBTS29 | |
| OFDS XVII | Autosomal recessive | 4q28.1 | INTU, KIAA1284, PDZK6, SRTD20, OFD17 | |
| OFDS XVIII| Autosomal recessive | 3q13.12-q13.13 | IFT57, ESRRBL1, HIPPI, OFD18 | |

Fig. 1. (A) Presence of multiple milia on both cheek, predominantly on the left side. (B) Presence of multiple milia in the cheek as well as auricle. Partial hypotrichosis was also noted. (C) Shows bifid tongue and short frenulum. (D, E) Clino-brachy-syndactyly of hand were presented. (F) Anomalous deformities of both toes were seen on X-ray.
reported in a number of cases. The incidence of the disorder is estimated to be between 1/50,000 and 1/250,000 live births. However, there is no definite consensus about classification of OFDS. Because overlap of the clinical features between subtypes is common, classification of a specific patient can be difficult. However, OFD1 can be distinguished from other types by its characteristic milia. Observed in about 30% of patients with OFD1, OFDS milia show a more extensive pattern than primary congenital milia. Although they sometimes disappear within the third year of life and leave scars, milia usually persist. In addition, because such large, deep lesions can cause greater aesthetic problems than other congenital milia, active treatment is required. Polycystic kidney disease (PKD) and central nervous system involvement are also commonly observed in up to 63% and 50% of patients, respectively, with OFD1. The presence of PKD strongly suggests OFD1. However, symptoms of PKD most often develop in adulthood (second and third decades), so the syndrome may not be evident until adulthood.

Of the various subtypes of OFDS, the most diverse genetic mutations have been identified in patients with OFD1. Frameshift, insertion, nonsense, missense, slicing, or genomic rearrangements of OFD1 gene have been reported in cases. However, study reported that OFD1 gene mutation was found in 81 of 100 OFD1 patients (81.0%) who had undergone genetic testing. In another study, the OFD1 gene mutation was negative, but some cases diagnosed as OFDS due to clinical features were also identified. According to those reports, group of characteristic clinical manifestations are important clue to presume a diagnosis of OFD1 in so far as the genetic mutation of OFD1 is found in limited cases.

Oculodentodigital dysplasia (ODDD) is also one of the diseases that may have clinical features similar to OFD1. However, unlike OFD1, ODDD can be distinguished in that it is characterized ophthalmic change, and gap junction protein alpha 1 (GJA1) gene mutation is the cause. In addition, several syndromes associated with chromosomal microdeletion and duplication may have clinical features similar to OFD1. Our patient was excluded from the fact that no problems were found on the microarray.

Consequently, significant skin findings are very important because of their usefulness in early diagnosis of OFD1. The patient in the present case was suspected of having OFD1 based on the characteristic clinical findings.

We described a rare case of OFD1 in a patient with congenital milia, which has never been reported in the Korean dermatologic literature. Continuous follow-up, including renal and brain evaluation, should be considered in patients with OFDS.

In conclusion, among the subtypes of OFDS, OFD1 is of significance to the dermatologist because its characteristic skin lesions can assist in differential diagnosis from other subtypes, and it requires active dermatological treatment.

CONFLICTS OF INTEREST

The authors have nothing to disclose.
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