A Case of Ankyloblepharon-ectodermal Defects-cleft Lip/Palate-syndrome with Choanal Atresia and Skin Erosions: Phenotypic Variability of *TP63*-related Disorders

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Ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome is an autosomal dominant disease. AEC was first described by Rapp & Hodgkin in 1968 in a family in which the patients presented the same clinical traits (1). Until now, differentiation between AEC and Rapp-Hodgkin syndrome (RHS) has been made by the presence of ankyloblepharon and midfacial hypoplasia, respectively (2, 3). However, as has been stated previously, differentiation between AEC and RHS should be abandoned in favour of a more inclusive term (4).

TP63 encodes the p63 protein, which is essential for the maintenance of epidermal stem cells. Furthermore, p63 takes part in the morphogenesis and maintenance of the epidermis. It regulates the proliferation and differentiation of keratinocytes. Mutations in *TP63* also cause other syndromes, such as acro-dermato-ungual-lacrimal-tooth syndrome (ADULT), ectrodactyly–ectodermal dysplasia–cleft syndrome (EEC syndrome), split-hand/split-foot malformation type 4 (SFHM4), limb-mammary syndrome (LMS) and isolated cleft lip/cleft palate (CL/P) (5).

CASE REPORT

A newborn girl was referred to the Center for Rare and Genetic Skin Diseases from the Department of Pediatrics of Harlaching, Municipal Hospital, Munich, Germany. She was the 2nd child of healthy, non-consanguineous parents of Caucasian origin, and was born at 41+1 weeks by vaginal delivery. At birth her weight was 3,530 g (45th centile), length 54 cm (79th centile) and head circumference 37 cm (91th centile). At birth, she presented with generalized erythema and widespread superficial skin erosions on the lumbosacral region (**Fig. 1**a). The girl had facial deformity, including midfacial hypoplasia, bilateral ectropion, small nasal bridge, long philtrum, microstomia and nail hypoplasia.

Despite the striking clinical findings, she was in good general health with no raised inflammatory markers. After 10 days she developed difficulty suckling. A nasal-gastric catheter could not be passed through the nostrils, therefore magnetic resonance imaging (MRI) was performed. This confirmed the presence of bilateral bony choanal atresia. Several surgical interventions were performed to correct the defect. Her renal function was normal, but a renal pelvis dilatation was identified, which could lead to urinary dysfunction or even obstruction. The lumbosacral erosions healed, but new erosions with crusts appeared on the fronto-parietal scalp (Fig. 1b). By 3 months the girl' growth was normal; length 57 cm (45th centile) and weight 5,180 g (29th centile).

At the age of 6 months the erosions on her scalp improved and white, wiry hair was observed. Trichoscopy revealed a lack of pigment. At the age of 11 months new erosions appeared on the scalp as well as diffuse alopecia (Fig. 1c). The fingernails and toenails had developed from hypoplastic (Fig. S1a, b[1]) to dystrophic (Fig. S1c[1]), and the appearance of dark pigmented teeth was noted (Fig. 1d). During follow-ups bacterial swabs were taken from the scalp and showed massive colonization with *Staphylococcus aureus*, which was treated with topical antibiotics (fusidic acid), in combination with betamethasone, and antiseptic measures with polyhexanide.

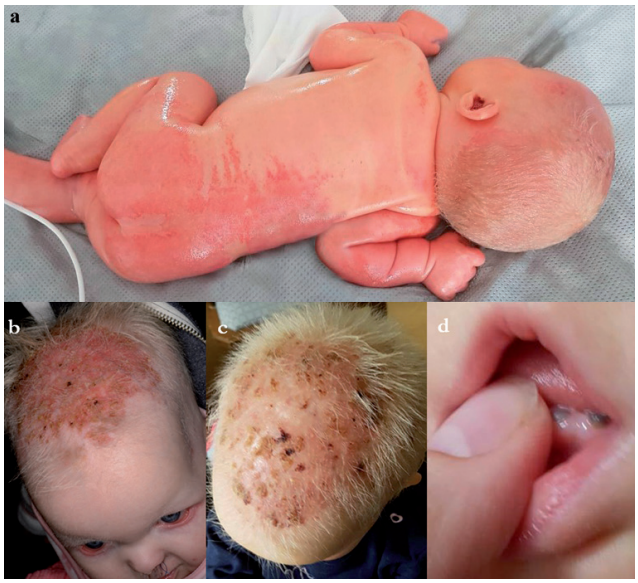

Fig. 1. (a) Generalized erythema of the skin and multiple erosions on the lumbosacral region. (b) Erosions of the scalp. (c) Erosions of the scalp with sparse, white wiry hair. (d) Dark pigmented teeth. Permission to publish these photographs are given by the patient's parents.

To summarize the clinical findings: the young patient presented at birth and at 1 month with skin erosions on the scalp, nail dysplasia, teeth anomalies, genitourinary deformities and choanal atresia (Table SI[1]). As in the first weeks, many of the clinical findings were not yet present, and because they could not be attributed to a specific syndrome, single exome sequencing was performed. The previously published heterozygous missense variant c.1790T>C, p.(Ile597Thr) was identified in the *TP63* gene, which has been described previously in a patient with AEC syndrome (5). The variant was not listed in 120,000 control alleles of the Exome Aggregation Consortium (ExAC)-Browser and it was predicted to change a conserved amino acid. The *de novo* status was confirmed by carrier testing of the unaffected parents. The variant could not be identified in blood DNA from the parents using Sanger sequencing.

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Blood samples were collected from the patient for exome sequencing and from her parents for Sanger sequencing, after obtaining written informed consent from the parents. DNA was extracted from peripheral blood using the Gentra Puregene Blood Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Exome sequencing of the patient's sample was performed by using a Sure Select Human All Exon 60Mb V6 Kit (Agilent Technologies, Santa Clara, CA, USA) for enrichment and a HiSeq 4000 sequencer (Illumina, San Diego, CA, USA), as described previously (6). Reads were aligned to the University of California Santa Cruz (UCSC) human reference assembly (hg19) with BWA v.0.5.8. More than 99% of the exome was covered at least 20×. *TP63* was covered >20× to 100%. Single-nucleotide variants and small insertions and deletions were detected with SAMtools v.0.1.7. Variant prioritization was performed based on an autosomal recessive pattern of inheritance (minor allele frequency <0.1) and an autosomal dominant pattern of inheritance (heterozygous variants with a minor allele frequency <0.001%).

DISCUSSION

The pathogenic variant c.1790T>C in the *TP63* gene, which was identified in our patient with AEC syndrome, has been reported previously in one case (5). However, this patient had no choanal atresia, but had a secondary cleft palate. Similarities between the two cases are the extensive skin erosions, background erythema and nail hypoplasia. Furthermore, in both cases the children presented massive erosions of the scalp, followed by a lack of hair growth. The other erosions on the body of the previously reported patient appeared to be superficial and there was no scarring observed. However, the child was followed up for only one year.

The association between AEC syndrome and choanal atresia, as presented in our patient, was reported to our knowledge only in two cases (7, 8).

The pattern of erosions presented in our patient is pathognomonic for AEC syndrome. The ones from the lumbosacral region were superficial, and the histology showed no pathological findings. The region healed and, at the last visit, no scars were visible. Erosions on the head tend to be more severe and often produce scars. Erosions on other body regions usually heal without scarring (3, 9, 10).

Our bacteriological findings sustain the previous reports of secondary colonization and infection with *S. aureus* and other Gram-positive and Gram-negative bacteria (9, 11). Patients commonly require intermittent systemic antibiotic therapy, due to frequent skin infections (3).

Mutations in the *TP63* gene are responsible for a variety of syndromes: AEC, ADULT, EEC, Limb-Mammary, SHFM4 or the isolated CL/P. All of these 6 known syndromes have multiple features in common (Table SI[1]) (12). This summary implies that the different entities are a single disorder with a range of disease severities. This hypothesis is also strengthened by the fact that published cases harbouring the identical mutation in *TP63* were more severely affected. Although we know that AEC syndrome has a wide phenotype, we consider that the clinical findings in our index case best match the diagnosis of AEC syndrome. However, many disease-associated features are absent, indicating that the differentiation of *TP63*-related disorders should be revised. The phenotypic spectrum of these conditions seems to be broad, as highlighted by the clinical variability of patients with the same mutation in *TP63*. Therefore, we consider that differentiation between these syndromes is artificial and the term "*TP63*-related ectodermal dysplasia" should be preferred.

In conclusion, patients with AEC should be clinically monitored over time. To avoid future infections skin erosions should be treated with antiseptic measures and, if necessary, topical antibiotics applied. AEC syndrome should be considered in cases of ectodermal dysplasia and skin erosions on the scalp and body. The diversity of phenotype and genotype correlation in p63-related disorders should be evaluated in a larger cohort.

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