CLINICAL REPORT

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A Newborn With Overlapping Features of AEC and EEC Syndromes

Tolga Hasan Celik,[1]* Ayse Buyukcam,[2] Pelin Ozlem Simsek-Kiper,[3] Gulen Eda Utine,[3] Sibel Ersoy-Evans,[4] Ayse Korkmaz,[1] Helger G. Yntema,[5] Koray Bodugroglu,[3] and Murat Yurdakok[1]

[1]Neonatology Unit, Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara, Turkey

[2]Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara, Turkey

[3]Pediatric Genetics Unit, Department of Pediatrics, Faculty of Medicine, Hacettepe University, Ankara, Turkey

[4]Department of Dermatology, Faculty of Medicine, Hacettepe University, Ankara, Turkey

[5]Department of Human Genetics, Radboud University, Nijmegen Medical Center, Nijmegen, Netherlands

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Ectrodactyly, ectodermal dysplasia, clefting (EEC) syndrome is the prototype of several *p63* conditions, which include ankyloblepharon, ectodermal dysplasia, clefting (AEC) syndrome, limb-mammary syndrome (LMS), Rapp-Hodgkin syndrome (RHS), ADULT syndrome, and others. All these disorders include combinations of ectodermal dysplasia, orofacial clefting and limb malformations in variable severity. A newborn patient is presented with diffuse erythematous and desquamating skin lesions and anal atresia. She also had sparse and lightly colored thin hair, deeply set eyes, hypoplastic alae nasi, and a short philtrum. Cleft lip/palate and ankyloblepharon were not present. Complete cutaneous syndactyly was present on both hands in between the 3rd and 4th fingers. Mild ectrodactyly was evident on all four extremities in between first and second digits. There was post-axial polydactyly on both feet. Anal atresia was present and defecation occurred through a rectovaginal fistula. The patient represented an interesting overlapping clinical condition between AEC and EEC syndromes. Diffuse skin lesions with excoriation and desquamation suggest AEC syndrome, despite the absence of ankyloblepharon, however; ectrodactyly and polydactyly strongly suggest the EEC syndrome. *C308Y* mutation in exon 8 of *TP63* gene was detected, which was previously described to lead only to EEC syndrome and not to any of the other allelic conditions. These data emphasize the large degree of clinical variability that may be seen for specific *TP63* mutations.

Key words: ectrodactyly; ectodermal dysplasia; clefting; ankyloblepharon; AEC; EEC; newborn

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INTRODUCTION

Anklyoblepharon-ectodermal dysplasia-cleft lip/palate (AEC) syndrome, also known as "Hay–Wells syndrome," is a rare, autosomal dominant disorder defined by ectodermal abnormalities of the skin, teeth, hair, and nails, in combination with characteristic eyelid fusion and facial clefting. Denuded skin leading to life-threatening sequelae can occur in affected infants. Persistent scalp and skin erosions, complicated by infection, are common features of this syndrome. The clinical findings of AEC syndrome can overlap with those of other ectodermal dysplasia (ED) syndromes and are variable in presentation, which complicates the diagnosis and further characterization of these disorders. AEC syndrome belongs to a group of diseases caused by mutations in *TP63* gene, which are characterized by ectodermal dysplasia, orofacial clefting, and split hand/foot malformation. Although there are significant phenotypical overlaps between these individual syndromes, there are also well-outlined mutation-specific and distinct phenotypes, even within each syndrome [Rinne et al., 2006]. Examples include R204 and R227 mutations which cause ectrodactyly, ectodermal dysplasia, clefting syndrome (EEC) mostly; however, absence of clefting, rare occurrence of limb defects and hearing impairment, frequent occurrence of urogenital problems and hypohidrosis characterizes patients with R227 mutations among others [Rinne et al., 2006]. R279 mutations are highly related to ectrodactyly, whereas R280

*Correspondence to:
Tolga Hasan Celik, Department of Pediatrics, Section of Neonatology Sihhiye, Faculty of Medicine, Ihsan Dogramaci Children's Hospital, Hacettepe University, Ankara 06100, Turkey.
E-mail: htcelik@yahoo.com

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mutations are frequently associated with skin signs and syndactyly, without hearing, kidney, and sweating problems [Rinne et al., 2006]. On the other hand, some mutations of *TP63* were reported to cause more than one syndrome; examples include limb-mammary syndrome (LMS) and EEC occurring due to R204Q and R227Q, EEC and split hand/foot malformation (SHFM) occurring due to R280 mutations, and AEC and Rapp-Hodgkin syndrome (RHS) caused by 1859delA, I510T. EEC and AEC syndromes were not previously described to have overlapping features. Except for two patients with EEC syndrome in whom R279 mutations were detected, ankyloblepharon was never described in EEC syndrome [Berdón-Zapata et al., 2004]. We report on a newborn who presented with overlapping clinical findings of AEC and EEC syndromes.

CLINICAL REPORT

A 3,000 g female infant born at term presented with diffuse erosions, erythema, and desquamation all over the body, particularly over her extremities and the scalp that existed from birth (Fig. 1a). She had sparse and lightly colored hair, hypoplastic alae nasi, and a short philtrum (Fig. 1b). Complete cutaneous syndactyly was present on both hands in between third and fourth fingers (Fig. 2). Mild ectrodactyly was evident on all four extremities in between first and second digits (Fig. 3). There was post-axial polydactyly on both feet. She had anal atresia with accompanying rectovestibular fistula. Neither cleft lip/palate, nor ankyloblepharon was present.

She was the fifth child of healthy nonconsanguineous parents. Her brother and three sisters were unaffected. On the second day of life she weighed 2,470 g (below 10th centile). She had severe dehydration with prerenal azotemia and hypernatremia. Dexpanthenol ointment, petrolatum ointment, mupirocin ointment, and Xeroform (3% Bismuth Tribromophenate) were applied for skin lesions. Rectovestibular fistula was intermittently dilated.

Abdominal, renal, and cranial ultrasonography revealed normal results. A secundum type atrial septal defect and patent ductus arteriosus were detected on echocardiographic examination. On the 28th day of hospitalization, she was discharged with a body weight of 2,640 g and significantly improved all skin lesions. Blood was drawn for mutation analysis for EEC syndrome. She died 1 month later in a local hospital due to sepsis.

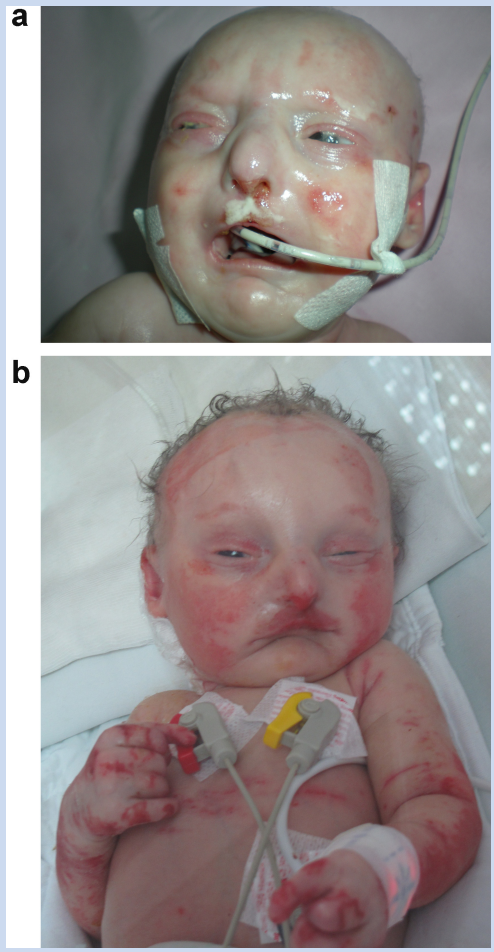

FIG. 1. A: Erosions over the face, hypoplastic alae nasi and short philtrum were noted immediately after the delivery. B: The same patient with diffuse erosions, erythema, desquamation all over the body, and sparse and lightly colored hair several days after the delivery.

Mutation Analysis

Mutation analysis revealed a heterozygous missense mutation *c.1040G > A* in the *p63* gene, which predicts an amino acid substitution *p.Cys347Tyr* in the DNA-binding domain of the *TP63* protein (mutation nomenclature refers to Refseq clone *NM_003722.4*, which corresponds to *C308Y* in former publications [Rinne et al., 2007]). Parental blood samples were not tested.

DISCUSSION

This patient presented with overlapping features of two allelic disorders; the ankyloblepharon-ectodermal defects-cleft lip/palate (AEC; OMIM 106260) and the ectrodactyly-ectodermal dysplasia and cleft lip/palate (EEC; OMIM 604292) syndromes. Those are ectodermal dysplasia syndromes which are caused by *TP63* mutation. Common features of the two conditions are ectodermal dysplasia and cleft lip/palate.

EEC syndrome is a prototype of numerous *TP63* syndromes. Characteristic limb malformations include ectrodactyly, polydactyly, and syndactyly. Additionally, light-colored, sparse hair, thin, and dry skin are noted in dermatological examination. Dystrophic nails and dental abnormalities may be seen [Rinne et al., 2007]. Anal atresia has been observed in EEC syndrome [De Smet and Fryns, 1995], but not in AEC syndrome.

AEC syndrome is characterized by ankyloblepharon and severe skin erosions at birth [Tsutsui et al., 2003]. Ectodermal dysplasia in AEC syndrome is more severe with skin erosions, alopecia, and nail and teeth defects in 75–80% of the patients. Ankyloblepharon, which helps in differentiating AEC from EEC when present, is observed in only 44% of patients with AEC syndrome. Likewise,

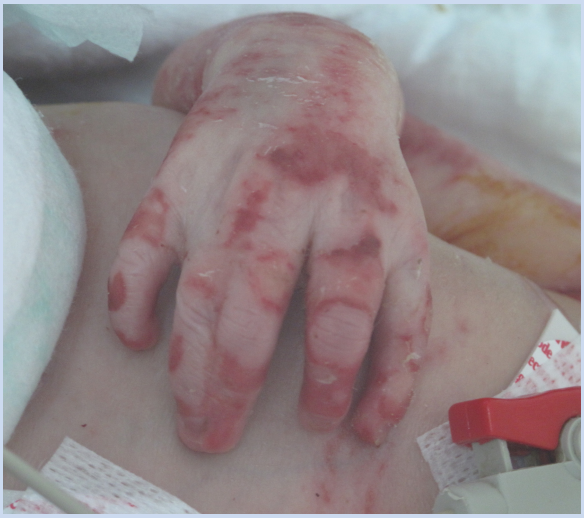

FIG. 2. Note complete cutaneous syndactyly between third and fourth fingers of right hand.

hearing loss may be helpful in differential diagnosis, since it is present in 40% of patients with AEC syndrome, but is uncommon in EEC syndrome [Rinne et al., 2006].

Limb malformations also differentiate the two allelic conditions. These are present in EEC syndrome, whereas they are usually mild in AEC syndrome. Several patients with AEC have been reported to have syndactyly [Rinne et al., 2006] and only two other AEC patients presenting with ectrodactyly have been reported previously

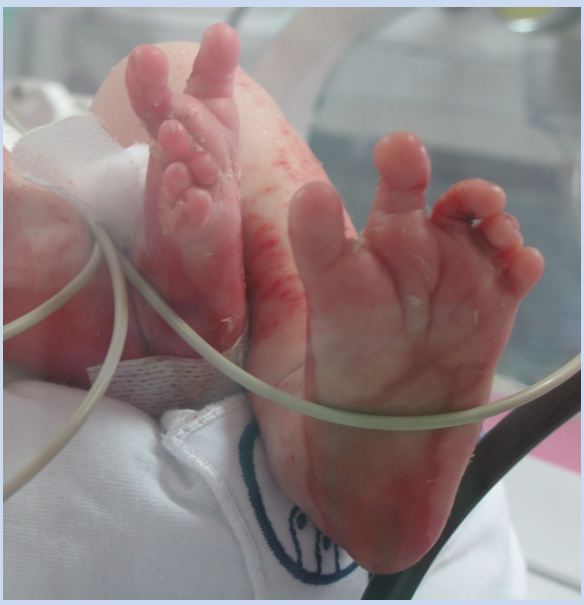

FIG. 3. Note ectrodactyly between first and second digits, and post-axial polydactyly of both feet.

[Sutton et al., 2009]. Our patient had syndactyly, polydactyly, and mild ectrodactyly. The third component of both syndromes is cleft lip/palate, which was absent in our patient. This finding is frequent in EEC syndrome, and is present in 80% of AEC syndrome patients [Rinne et al., 2006].

The present patient represented with an overlapping clinical features of AEC and EEC syndromes. Neonatal presentation with diffuse skin erosions was suggestive of AEC syndrome, despite the absence of an ankyloblepharon, however; presence of severe limb anomalies like ectrodactyly and polydactyly are more common in EEC syndrome. Clinical overlap may be present among allelic disorders caused by *TP63* mutations, however, this patient is remarkable in that she represents an overlapping condition between EEC and AEC syndromes.

Currently researchers have described 74 different mutations in the *TP63* gene, causing five syndromic and two nonsyndromic allelic disorders. Clear genotype–phenotype correlation have been established for *TP63*-related disorders. In general, mutations clustered in the DNA binding domain lead to EEC syndrome, whereas mutations in the *SAM* and *TI* domains cause AEC/Rapp Hodgkin syndrome [Bougeard et al., 2003]. However, some mutational overlap exists between these seven allelic conditions [Rinne et al., 2007]. Although there is always a risk for a possible misdiagnosis among these related clinical disorders, it is also well-known that phenotypic variation within one disorder and even within each affected family may exist. This variation may reflect the effects of modifiers, highly diverse cellular functions of this developmental gene, or its expression in several isoforms.

The current mutation has never been detected in individuals with AEC syndrome. Missense mutations affecting *cysteine 347/308* have been previously reported in two individuals diagnosed with EEC syndrome [van Bokhoven et al., 2001; Rinne et al., 2007]. One mutation was exactly the same as in the present case (*C308Y*), whereas the other individuals with EEC syndrome had a substitution *C308S*. This amino acid is located in the DNA-binding domain of the protein, where mutations typically cause EEC syndrome [Rinne et al., 2007]. An exception to this is *R279H* mutation in this domain. *R279H* is a hotspot mutation for EEC syndrome, but has also been reported in one patient with an AEC-syndrome-like phenotype [Bougeard et al., 2003]. The *C308S* mutations constitute a second example where amino acid substitutions may give rise to either EEC syndrome or a phenotype that has features of both EEC and AEC syndrome. Thus, our data substantiate the notion that a large degree of clinical variability can be observed for specific *TP63* mutations [Rinne et al., 2006].

This case represents overlapping phenotypes of EEC and AEC syndromes, caused by a mutation in the DNA-binding domain of *TP63*. While this mutation would be expected to result in a phenotype more consistent with EEC, the severe skin erythroderma are more typical of AEC. Anal atresia seen in this individual, has been reported in EEC but not AEC. Thus this case seems to represent a rare overlap of phenotypes AEC and EEC syndromes.

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