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Ectrodactyly-Ectodermal Dysplasia-Clefting Syndrome (EEC): Report of a Case with Perioral Papillomatosis

Bárbara Fernandes, M.D., Evelina Ruas, M.D., Álvaro Machado, M.D., and Américo Figueiredo, Ph.D.

Department of Dermatology, Hospitais da Universidade de Coimbra, Coimbra, Portugal

Abstract: **We report a 13-year-old boy with ectodermal dysplasia, ectrodactyly, and syndactyly, hypospadias, photophobia, conductive hearing loss, and perioral papillomatosis. His father had ectrodactyly and hypotrichosis. The clinical picture suggested ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome. The presence of perioral papillomatosis, classically seen in Goltz syndrome, has been reported only once before in EEC syndrome.**

Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome is an autosomal dominant, complex, pleiotropic, multiple congenital anomaly (1). This acronym was first used by Rudiger et al (2) in 1970, although cases with similar anomalies had previously been reported. The most common clinical manifestations (1,3–5) are ectodermal dysplasia (categories 1–4) (6), ectrodactyly, cleft lip/palate, and tear duct anomalies (atresia/hypoplasia of the lachrymal duct/puncta and consequently constant tearing, blepharitis, conjunctivitis, epiphora, corneal opacities, and photophobia).

The ectodermal component of this syndrome involves the hair (hypotrichosis and hypopigmentation, so the scalp hair, eyebrows, and eyelashes might be sparse, fair, and dry), teeth (hypodontia, microdontia, and enamel dysplasia), and nails (dystrophic in most cases). Hypohidrosis (4,5) is variable. Other manifestations include urogenital anomalies (kidney and ureter malformations, urinary reflux, hypospadias, and cryptorchidism), mental retardation, nipple anomalies, comedone nevus (7), choanal atresia (8), a reduced number of meibomian orifices (9), variable minor ear anomalies, conductive hearing loss, breathy voice, hypopituitarism, and isolated growth hormone deficiency (10).

The phenotype of the EEC syndrome may vary considerably. The most constant finding is ectodermal dysplasia, which was found in all 123 patients reviewed by Rodini and Richieri-Costa (1), whereas 84% had tear duct anomalies, 83.7% ectrodactyly, 72.4% cleft lip/palate, 33.3% genitourinary anomalies, 14% deafness, and 6.6% mental retardation.

This condition is presumed to have an autosomal dominant inheritance with incomplete penetrance and variable expression. Sporadic cases also occur. Mutations in the p63 gene have recently been delineated as the molecular basis for some cases of the EEC syndrome (11). Identification of this mutation has implications for genetic counseling and the feasibility of future DNA-based prenatal diagnosis.

CASE REPORT

A 13-year-old boy was born at term after an uncomplicated pregnancy to a 24-year-old, healthy mother

Address correspondence to Bárbara Fernandes, M.D., Serviço de Dermatologia dos Hospitais da Universidade de Coimbra, Praceta Prof. Mota Pinto, 3000-075 Coimbra, Portugal.

and a 38-year-old father. He was the only child of unrelated parents, and there was no history of previous abortions. At birth he had hypospadias, ectrodactyly, and syndactyly affecting both hands and feet (Fig. 1). Various anomalies, such as hypodontia and microdontia (Fig. 2), ungual dystrophy (Fig. 1), hypotrichosis, dry skin, sparse, fair, and dry scalp hair, sparse eyebrows, and papillomatosis of the lips (Fig. 2), were noted during his first years of life. He was in the 25th percentile for weight and 50th for height and had learning disabilities.

Ophthalmologic examination revealed a reduced number of meibomian orifices. The nasolacrimal duct was patent. The audiologic examination revealed a discrete conductive hearing loss. Laboratory findings were normal, including VDRL and hormone levels (ACTH, cortisol, GH, free and total testosterone, FSH, LH, T_3, T_4, TSH). Skeletal radiograph revealed the expected absence of some dactylic segments and the fusion of others. Panoramic film showed hypodontia with wrongly implanted teeth. Abdominal ultrasound, including kidney observation, was normal. Karyotype was also normal, but DNA diagnosis was not performed. A biopsy specimen from a papillomatous lesion showed papillary hyperplasia of the mucosa, neutrophilic exocytosis, and dilated capillaries, some of which were filled with erythrocytes. Special stains for fungi were negative. The patient had no clefting of the lip/palate or tear duct abnormalities, but we think the absence of these features does not compromise the diagnosis of EEC syndrome, which has variable expression. Besides, these two features usually coexist, probably because of their anatomic proximity (1).

His father, who died at the age of 48 years of esophagus cancer, also had ectrodactyly and hypotrichosis, but apparently no other features of the syndrome. No other family members were known to be affected.

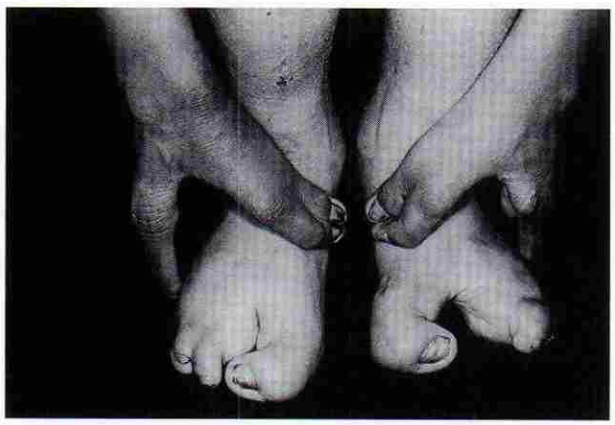

Figure 1. Hands and feet show ectrodactyly and syndactyly as well as dystrophic nails.

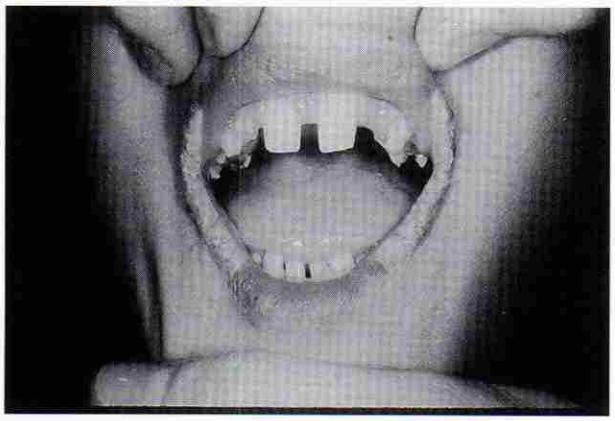

Figure 2. Hypodontia and microdontia. Papillomatous lesions are seen at the commissures of the lips.

DISCUSSION

EEC syndrome is a very rare condition, and we consider this case even more interesting since, to the best of our knowledge, it is only the second report of papillomatous lesions in EEC syndrome (12). Perioral papillomatosis is, however, clinically associated with Goltz syndrome (13), also called focal dermal hypoplasia. The clinical expressions of EEC syndrome and Goltz syndrome are quite variable, and many clinical signs are common to both, namely ectodermal dysplasia (categories 1–4) (6), clefting, acral defects, tear duct anomalies, genitourinary anomalies, and hearing loss (14) (Table 1).

Nevertheless, the clinical spectrum of the Goltz syndrome is usually wider than that of the EEC syndrome,

TABLE 1. *Main Findings in EEC Syndrome, Goltz Syndrome, and Our Patient*

	EEC syndrome	Goltz syndrome	Our patient
Inheritance	Autosomal dominant	X-linked dominant	Autosomal dominant
Nail dysplasia	+ +	+	+ +
Dental anomalies	+ +	+	+ +
Sparse, thin hair	+ +	+	+ +
Ectrodactyly	+ +	+	+ +
Clefting	+ +	+	–
Tear duct anomalies	+ +	+	–
Limb anomalies	+ +	+	+ +
Hypoplasia of the dermis	–	+ +	–
Papillomatous lesions	–	+ +	+
Mental retardation	+	+ +	+
Osteopathia striata	–	+ +	–
Genitourinary defects	+ +	+ +	+
Cardiac defects	–	+	–
Hearing loss	+	+	+

The number of pluses (+) refers to the frequency of involvement.

and typically includes skin defects such as atrophic areas in a cribriform or reticulated pattern, with fat herniations, focal eroded lesions with total absence of the epidermis and dermis, scars, telangiectasia, and papillomatosis, which are the most common manifestations of this entity. Goltz syndrome also has characteristic radiologic findings that include osteopathia striata, which are asymptomatic, fine, linear, radiopaque densities in the metaphyses of the long bones. Most cases occur in females and inheritance is thought to be X-linked; it is usually lethal in male hemizygotes.

Although the designation of EEC suggests only ectrodactyly, ectodermal dysplasia, and cleft lip/palate, numerous abnormalities are associated with this rare autosomal dominant entity and perhaps we can include among them the presence of papillomatous lesions.

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