Corneal Findings in Ectrodactyly Ectodermal Dysplasia Clefting Syndrome: Case Report and Literature Review

Abstract
The purpose of this study was to report the ocular findings in an unusual case of ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome and review the etiology and clinical presentation of similar situations in the literature. This study is an observational case report of a 13-year-old woman with complaints of epiphora and red eye. On examination, she presented with lachrymal punctal agenesis and neo-vascularization in both eyes. She was treated medically and without any surgical intervention. Corneal changes in EEC can have a variable presentation. The etiology of such keratopathy seems to be due to several factors and limbal stem cell deficiency (LSCD) being the newest factor involved. Recurrent infection from lachrymal drainage obstruction and tear film instability are other risk factors for disease severity and progression. Since these patients present several anomalies, it is important, to follow an interdisciplinary approach to reduce complications and provide the best possible medical care.

KEYWORDS: Ectrodactyly-ectodermal dysplasia-clefting syndrome; Lachrymal anomalies; Blepharoconjunctivitis; Keratopathy; Limbal stem cell deficiency.

INTRODUCTION
Ectrodactyly-ectodermal dysplasia cleft lip/palate (EEC) syndrome is a rare genetic disorder, as being between 1 in 10,000 and 1 in 100,000 births.1 The majority of cases are reported to be autosomal dominant with variable expression and penetrance. This disorder is characterized by a triad of clefting deformity of the hands and feet (ectrodactyly lobster claw deformity), ectodermal dysplasia, and facial clefting.2 The exact incidence and prevalence in the general population is unknown. Most cases of EEC syndrome are caused by mutations in the TP63 gene, located on the long arm of chromosome 3 (3q27). In rare cases, individuals with EEC syndrome carry chromosomal deletions or translocation on the long arm of chromosome 7 (7q11.2-q21.3). When EEC syndrome is caused by mutations in the TP63 gene is referred to EEC syndrome type 3 (EEC3), and when it results in chromosomal abnormalities of chromosome 7, it is known as EEC syndrome type 1 (EEC1).3 The signs and symptoms of affected individuals are highly variable, even among members of the same family. The features of ectodermal dysplasia include hypopigmented skin and hair, dystrophy of the nails, abnormal teeth, and lack of sebaceous glands. Other clinical features consist of urinary tract abnormalities, inguinal hernia, conductive hearing loss, and mental retardation.4,5 The reported ocular anomalies are strabismus, fused lids at birth, entropion, an absence of eyelashes, bilateral eyelid cysts, absence or atresia of the lachrymal drainage system and meibomian gland dysfunction. The ophthalmological problems are responsible for a wide variety of ocular surface disorders, such as recurrent corneal erosions, corneal opacification, vascularization, and perforation. The cause of such ocular surface disorders in EEC syndrome is still unclear.6,7

We report herein the ocular findings of a patient with EEC syndrome and review the possible etiology and clinical presentation of similar situations in the literature.

CASE REPORT
A 13-year-old Caucasian female previously diagnosed with EEC syndrome was evaluated due to epiphora and conjunctival hyperemia.
She was born with cleft lip and missing digits in both hands and feet. She also had sparse hair, hearing loss, dental abnormalities, lachrymal punctal agenesis and factor VII (FVII) deficiency. She had undergone corrective surgeries for her cleft lip and palate as well as for hands and feet. Her ocular history was significant for chronic blepharoconjunctivitis in both eyes. On examination, her best-corrected visual acuity (BCVA) was 20/30 in both eyes. Slit-lamp examination revealed mild blepharitis and meibomitis, sparse eyelashes, an absence of upper and lower lachrymal puncta (Figure 1) and mild conjunctival hyperemia. Both corneas showed superficial pannus superiorly and inferiorly (Figure 2). Mild stromal scarring and lipid deposition was present on the leading edge of the pannus in both eyes, but it is more severe in the right cornea. A detailed examination of the left cornea revealed para-central stromal scarring near the visual axis (Figure 3). There was no epithelial defect on fluorescein staining. Schirmer’s test, tear break-up time and tear lakes were normal for both eyes. The remaining ophthalmological examination was unremarkable in both eyes. She was managed with hypromellose drops four to six times per day, hypromellose gel at bedtime and warm compress for twice daily. Currently, she maintains follow-up for evaluation of ocular symptoms.

DISCUSSION
EEC syndrome is a rare condition first characterized in 1970 by Rüdiger et al. as a triad of ectrodactyly of the extremities, ectodermal dysplasia, and facial clefting. Disruption of the development of embryonic ectoderm has been implicated in this syndrome, explaining the constellation of signs and symptoms. Ocular tissues are often involved in EEC syndrome. Patients can have varying combinations of ocular pathology ranging from dry eyes secondary to decreased lachrymal and meibomian gland secretion, blepharitis, conjunctivitis, dacryocystitis from lachrymal duct anomalies, to severe corneal pannus, scarring, and ulceration. Most of the affected ocular structures are derived from the ectoderm so it is not unexpected to see such features in a condition with widespread ectodermal dysplasia. Despite lachrymal anomalies have been cited as a fourth major distinguishing feature of EEC syndrome and many previous case reports have dealt extensively on the lachrymal system involvement in EEC, only a few have commented the corneal findings.

In this report, we present a patient with EEC syndrome and associated corneal findings. On the date of clinical observation, she exhibits a relative asymptomatic keratopathy with superior and inferior pannus and a corneal scarring in her left eye.

The etiology of the corneal pathologies seen in EEC remains unclear. Since the description of the disease, several studies have tried to demonstrate possible factors that explain corneal findings. In the early 1970s, Kaiser-Kupfer and Weigmann and Walker attributed the corneal changes to persistent infections secondary to a defective lachrymal drainage system. Another possible causative factor, demonstrated by Wilson et al, is tear film instability secondary to reduced lachrymal and Meibomian gland function.
Since the cornea is partially derived from the ectoderm, some authors believe that the corneal abnormalities seen in EEC are a manifestation of the ectodermal dysplasia itself. In 1997, Kasmann and Ruprecht hypothesized that the corneal scar formation was not due to a single causative event but secondary to several contributory factors, namely recurrent blepharitis, and conjunctivitis, tear film abnormalities and corneal epithelial dysfunction as part of ectodermal dysplasia.

Further studies have proposed limbal stem cell deficiency (LSCD) as a possible cause for corneal anomalies seen in ectodermal dysplasia. In the first reported, in 1997 by Tijmes et al., they performed limbal biopsy and impression cytology in patients with EEC and associated severe corneal neovascularization. The exams showed absent stem cells but failed to demonstrate the presence of goblet cells. They suggested that the corneal neovascularization was primarily due to the stem cell dysfunction. Most recently, in 2012, Di Iorio described the ocular phenotype of 23 patients with EEC syndrome. According to their study, EEC is caused by heterozygous missense mutations in the DNA-binding domain of the p63 gene, an important transcription factor during embryogenesis and stem cell differentiation of stratified epithelia. Fourteen cases (61%) were diagnosed with LSCD as evidenced by the absence of limbal palisades of Vogt on slit-lamp examination. They hypothesized that p63 mutation resulted in LSCD that lead to progressive keratopathy, the leading cause of visual morbidity in EEC patients. All patients were noted to have an anomaly of the meibomian glands, and 21 had lachrymal drainage system defects.

Since we do not have any histopathology to confirm LSCD, we attribute the corneal changes in this case to several contributory factors. This patient had blepharitis probably secondary to lachrymal duct anomalies, bilateral corneal pannus secondary to LSCD and corneal dysfunction presented as stromal scarring as part of ectodermal dysplasia itself.

In conclusion, this case report shows different ocular findings in a patient with EEC. The corneal changes can have a variably presentation. Chronic blepharoconjunctivitis and tear film abnormalities are contributory should be adequately treated to prevent disease progression. Since these patients present several anomalies, it is important, according to their phenotypic characteristics, to follow an interdisciplinary approach to reduce complications, to minimize undesirable sequelae and provide the best possible medical care.

REFERENCES

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