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Giant Ocular Lipodermoid Cyst in Encephalocraniocutaneous Lipomatosis: Surgical Treatment and Genetic Analysis

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Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 11
Final Diagnosis: Encephalocraniocutaneous lipomatosis
Symptoms: Conjunctivitis • Ocular irritation
Medication: —
Clinical Procedure: Excisional biopsy
Specialty: Ophthalmology

Objective: Rare disease

Background: Encephalocraniocutaneous lipomatosis is a rare neurocutaneous disorder characterized by cutaneous, ocular, and central nervous system anomalies; its molecular etiology was recently identified. This report describes the surgical treatment and genetic characterization of a giant ocular lipodermoid cyst secondary to encephalocraniocutaneous lipomatosis.

Case Report: An 11-year-old girl with past medical history of absence seizures presented with a reddish protruding mass in her right eye involving the temporal conjunctiva and the peripheral temporal cornea; eyelid closure was not possible due to mass protrusion. She also presented skin tags at the level of the external canthus and 3 alopecic areas at the level of the scalp compatible with nevus psiloliparus. No family history was reported. A dermoid cyst was suspected and excisional biopsy was performed under general anesthesia. A large conjunctival and lamellar corneoscleral resection was done, followed by a corneal tectonic graft. Molecular analysis was carried out, including PCR and Sanger sequencing on DNA obtained from the mass. After surgery, the patient achieved complete eyelid closure, reduction of ocular surface symptoms, and improved aesthetic appearance. Histological analysis confirmed a lipodermoid cyst; genetic tests confirmed a mosaic activating mutation in *FGFR1* (c.1638C>A, p.Asn546Lys). The diagnosis was encephalocraniocutaneous lipomatosis.

Conclusions: ECCL is a rare condition; an accurate diagnosis comprising clinical and genetic aspects can facilitate the monitoring of possible complications, improve the multidisciplinary treatment, and provide valuable information for future therapy developments. In this case, the patient's quality of life improved significantly, ocular symptoms disappeared, and a good esthetic appearance was achieved.

MeSH Keywords: Conjunctival Diseases • Corneal Diseases • Dermoid Cyst • Lipomatosis

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Background

Encephalocraniocutaneous lipomatosis (ECCL, OMIM #613001) was first described in 1970 by Haberland and Perou [1]. It is a rare neurocutaneous disorder characterized by cutaneous, ocular, and central nervous system anomalies, of which the most frequent are ocular choristomas, nevus psiloliparus (a well-demarcated alopecic fatty tissue nevus on the scalp), and intracranial/intraspinal lipomas [2]. Ocular choristomas (epibulbar dermoid and lipodermoid) occur in 80% of ECCL cases [3], and while their treatment is usually conservative, surgery is elected for those cases associated with recurrent conjunctivitis, amblyopia not responding to medical treatment, visual axis involvement, inadequate eyelid closure, or for esthetic considerations [4].

Over the past 50 years, since ECCL was first described, about 75 cases have been reported in the scientific literature. Recently, Bennett et al. identified 2 mosaic activating substitutions (p.Asn546Lys and p.Lys656Glu) within the cytoplasmic tyrosine kinase domain of fibroblast growth factor receptor 1 (*FGFR1)* that caused ECCL. These changes lead to a constitutive activation of mitogen-activated protein kinases (MAPK), which explains the different manifestations of ECCL [3]. Some ECCL patients also present mosaic KRAS mutations [5], and because these FGFR1/KRAS mutations are mosaics, they are only identifiable in diseased tissues but not in blood.

In this report, we describe a case of a giant ocular lipodermoid secondary to ECCL and the undertaken surgical approach. To the best of our knowledge, this is the first report to focus on the surgical management of a giant ocular dermoid associated with ECCL. Additionally, we carried out genetic analyses in the ocular tissue to obtain molecular confirmation of the diagnosis.

Case Report

An 11-year-old girl with past medical history of absence seizures since 6 months of age presented to our cornea department with a mass in her right eye. This mass was detected at birth and it slowly grew to the point of not allowing eyelid closure, causing exposure of the mass, focal irritation, and recurrent conjunctivitis. Cognitive and neural development had been normal.

Physical examination revealed mild facial asymmetry due to frontal prominence and 3 alopecic areas at the level of the scalp compatible with nevus psiloliparus (Figure 1A). The right external cantus had 2 small skin tags (Figure 1B). Visual acuity in the right eye (OD) was 20/400 both with (+10.50–6.75×35º) and without correction, and in the left eye (OS) it was 20/20. At biomicroscopy, the OD showed a protruding reddish mass that involved the temporal conjunctiva and extended to peripheral cornea from VI to IX meridians (Figure 1C). Complete eyelid closure was not possible due to mass protrusion (Figure 1D). Additionally, 2 areas of flat peripheral conjunctivalization were observed at XII and III corneal meridians (Figure 1C). On fundus examination, an optic nerve coloboma was noted. Biomicroscopy and fundus of left eye were within normal limits.

Ultrasound biomicroscopy (UBM) and anterior segment optical coherence tomography (AS-OCT) (TRITON, Topcon Medical Systems, Inc., Oakland, NJ, USA) were done and showed partial involvement of the cornea and the sclera (Figure 1E). Computed tomography of the orbits was performed and, besides the right orbital mass, an arachnoid cyst in the right temporal fossa and an intracranial lipoma at the level of right cerebellopontine angle were identified (Figure 1F).

Due to chronic irritation, esthetic appearance, and inadequate lid closure, a decision was made to perform surgical removal of the mass. An excisional biopsy was carried out under general anesthesia. The involved conjunctiva was resected and delimitation of the involved cornea was performed with a diamond ophthalmic knife set at 300 microns, trying not to affect the visual axis. Lamellar dissection of the involved cornea and sclera was done using a crescent blade and mitomycin C (MMC) 0.02% applied for 2 min over the scleral area. Tectonic cornea was used for reconstruction of the ocular surface; an 8.5-mm trephination of the donor cornea was performed and the button was manually cut over the resection area to achieve a similar shape. The resulting graft button was sutured with 10/0 nylon. The remaining healthy conjunctiva was advanced to the edge of the tectonic graft (Figure 2).

The removed tissue was divided into 2 halves; one half was fixed in formaldehyde and sent to the pathology laboratory, and the other half was submitted for genetic analysis. Histopathological hematoxylin-eosin staining analysis showed dense collagen tissue accompanied by some glandular lobes, increased vasculature, and lipid deposits (Figure 3). These findings supported the diagnosis of a lipodermoid cyst.

For genetic analysis, DNA was isolated from tissue samples of epibulbar dermoid biopsy. The coding regions of *KRAS* and *FGFR1* genes and their adjacent intronic sequences were amplified by PCR using pairs of primers corresponding to Ensembl reference sequences (*KRAS*, ENST00000311936.7; *FGFR1*, ENST00000447712.6). Direct automated sequencing of exons of *KRAS* and *FGFR1* was performed with the BigDye Terminator 3.1 Cycle Sequencing kit (Applied Biosystems, Foster City, CA). All samples were analyzed either on an ABI 3130 or a 3500xl Genetic Analyzer (Applied Biosystems) and sequences were compared against the respective reference sequences. Genetic analysis disclosed a mosaic heterozygous

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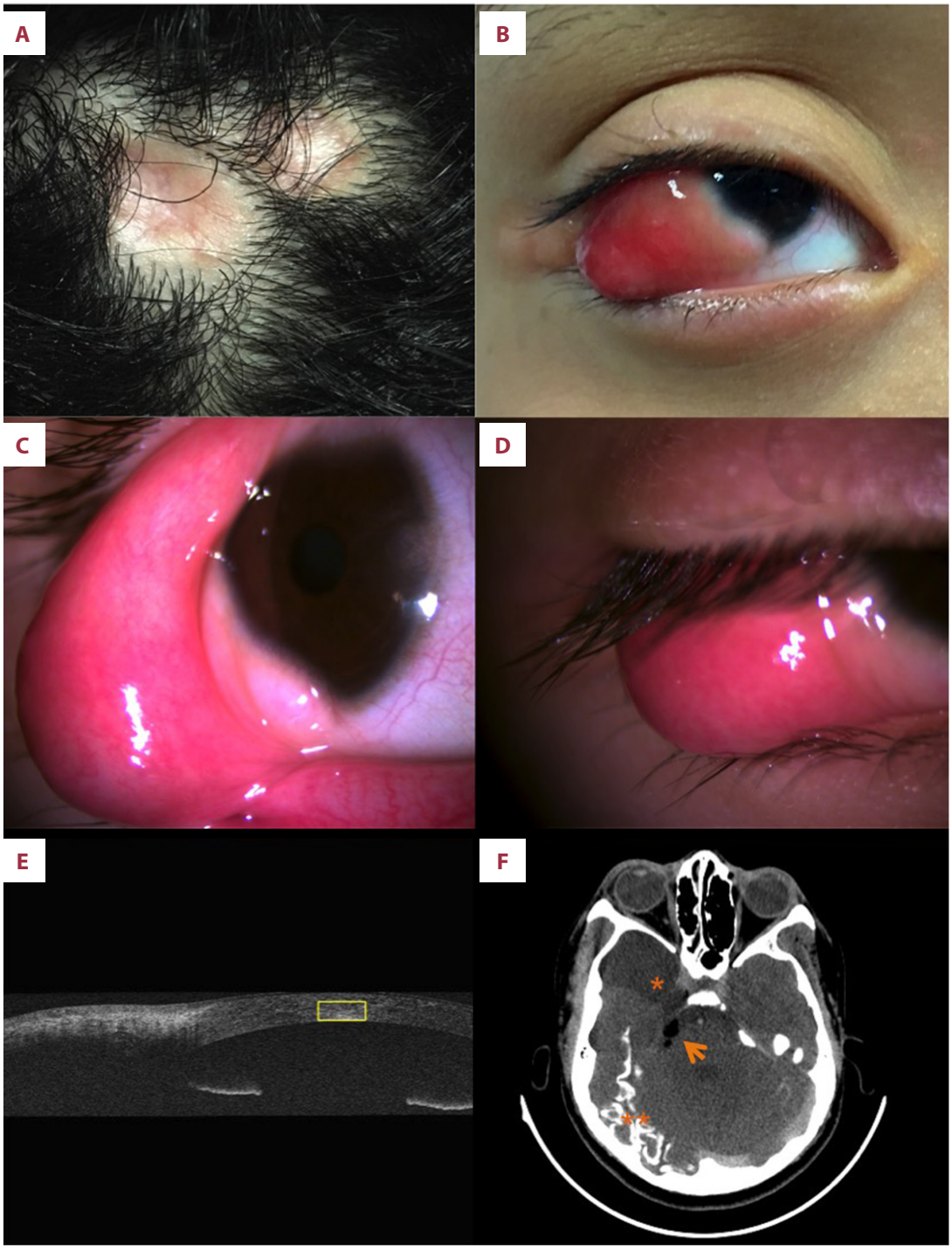

Figure 1. Ocular and intracranial findings. (**A**) Possible nevus psiloliparus at the level of the scalp. (**B**) Right eye. Macroscopic photograph shows 2 skin tags at the level of the external canthus and a reddish protruding mass. (**C**) Slit-lamp photography showing a protruding mass involving the temporal conjunctiva and extending to peripheral cornea from VI to IX meridians without compromising the visual axis. Two areas of flat peripheral conjunctivalization can be observed at XII and III corneal meridians. (**D**) Eyelid closure is not possible due to mass protrusion. (**E**) AS-OCT reveals partial involvement of the cornea. (**F**) Computed tomography of the orbits shows an arachnoid cyst (*) in the right temporal fossa, an intracranial lipoma at the level of right cerebellopontine angle (arrow), and some calcifications (**).

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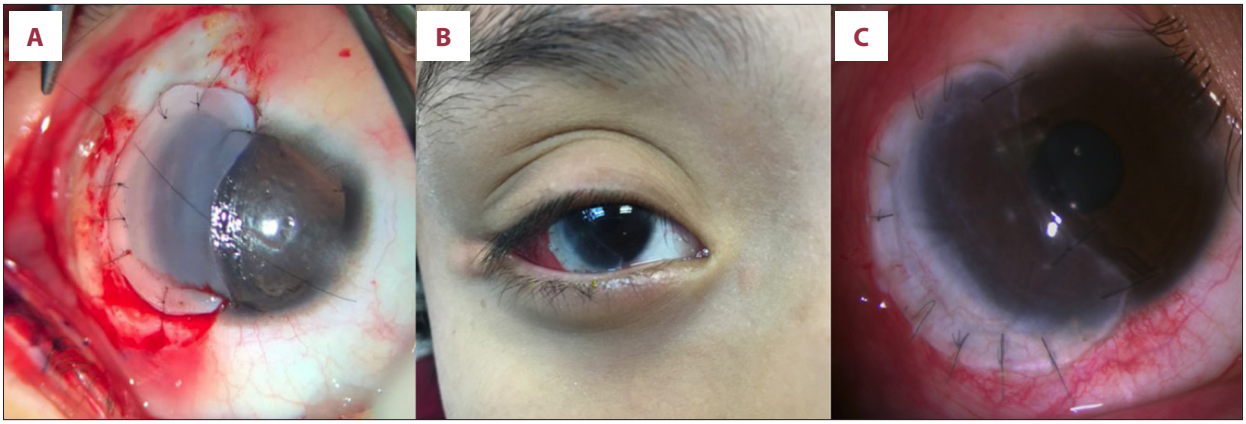

Figure 2. (**A**) Intra-surgical image: The complete resection was done and tectonic graft was used for ocular surface reconstruction. (**B**) Macroscopic view 16 weeks after surgery. (**C**) Slit-lamp photography 16 weeks after surgery.

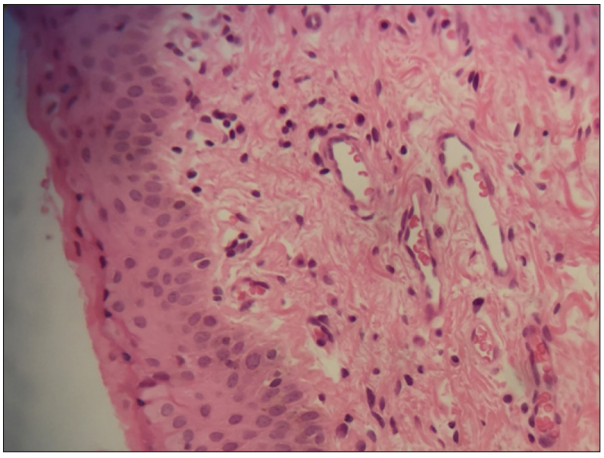

Figure 3. Histological characterization of ocular tissue. Hematoxylin-eosin staining (40×). Examination discloses dense collagen tissue accompanied by some glandular lobes, a great vasculature increase, and lipid deposits.

transversion c.1638C>A, predicting a p.Asn546Lys in exon 12 of *FGFR1* gene (Figure 4A). Analyses for *KRAS* and *FGFR1* genes were also performed in blood samples, but no alterations were found (Figure 4B). The percentage of mosaicism in the identified pathogenic variant was 26.8%; the estimation was done using the Mutation Surveyor program, which compares the area under the curve of wild-type electropherograms in blood and the mutated electropherograms from epibulbar tissue.

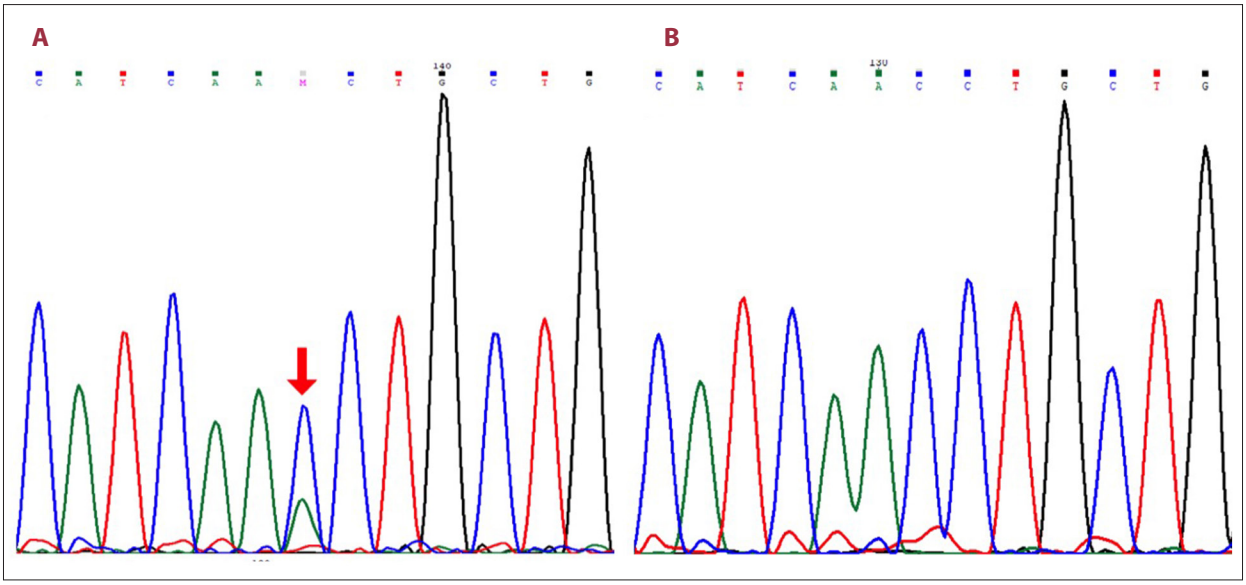

Figure 4. (**A**) DNA partial sequence showing the heterozygous mutation c.1638C>A (p.Asn546Lys) from the patient's dermoid tissue. (**B**) DNA partial sequence (control) from the patient's blood sample.

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Table 1. Clinical findings related to ECCL presented by the patient.

Ophthalmologic	Dermolipoma Hypertelorisms
Cutaneous	Possible nevus psiloliparus* Skin tags
Neurological	Intracranial lipomas Arachnoid cysts Seizures

* Not confirmed by biopsy.

The patient was diagnosed with ECCL on the basis of clinical (Table 1) and genetic findings. Post-operative follow-up has now been carried out for 6 months. Currently, the patient is able to close her eyelid completely and is satisfied with the achieved esthetic result. Visual acuity has not changed after the procedure (20/400 both with and without correction) given that the affected eye was amblyopic.

Discussion

ECCL is an uncommon condition in which most cases exhibit ophthalmologic manifestations [2]. We consider this case especially valuable for 2 reasons. First, it was from ocular tissue that the genetic diagnosis was made. Second, the giant size of the lesion represented a surgical challenge. These 2 considerations are discussed below.

According to the revised criteria proposed by Moog in 2009 [6], our patient presented clinical manifestations of a definitive case of ECCL, because it involved 3 systems and met 3 major criteria (lipodermoid cyst, intracranial lipomas, and possible nevus psiloliparus plus periocular skin tags). In this case, the 3 alopecic areas at the level of the scalp were compatible with nevus psiloliparus (possible nevus psiloliparus), but this manifestation could not be completely differentiated from aplasia cutis (also a possible feature of ECCL) without a skin biopsy to prove the diagnosis (proven nevus psiloliparus) [7]; however, a skin biopsy was not performed because it was not necessary for diagnosis and the lesions were completely asymptomatic.

Even if clinical diagnosis is possible, genetic confirmation is highly valuable since *FGFR1* mutations lead to constitutive activation of MAPK pathway and may thus increase the risk of neoplasm development [3,8].

ECCL is caused by somatic mosaic mutations, so samples from peripheral blood and/or unaffected tissues are unsuitable to detect such mutations; hence, the need for genetic analyses on DNA extracted from the affected tissues [3]. Normally, when there is dermatological involvement, the skin is the most accessible tissue for performing biopsy and obtaining DNA for exon sequencing. However, in the absence of cutaneous involvement or in cases with surgical indication for choristoma, the ideal is to carry out the study in ocular tissue. The mutation p.Asn546Lys of FGFR1 gene is a recurrent change that has been previously reported in Mexican patients [5], and it was found in the excisional biopsy tissue of our patient.

The dermoid presented by our patient was classified as grade 3 dermoid due to its size and according to the Visual Scoring System for Limbal Dermoid proposed in 2018 by Zhong et al. [9]. Therefore, it represented a surgical challenge because most surgical techniques described [4,10–12] have been evaluated only in lower-grade dermoids.

A deep lamellar corneoscleral keratoplasty was performed because this technique has been reported as safe and offers good appearance and tectonic stability [10,11]. A tectonic cornea was used to cover the entire corneoscleral resection area. The cornea represents an excellent tectonic tissue; when it is in contact with the patient's healthy endothelium, the cornea achieves excellent clarity and good esthetic results. In addition, unlike corneoscleral rims, tectonic corneas provide more viable tissue, which is of special importance for extensive resection. The conjunctiva was advanced only to the edge of the graft to serve as a limit and to avoid pseudopterygium formation.

Of note, because the treated eye was amblyopic, our priorities were esthetic and functional rather than refractive. Thus, the visual axis was avoided during surgery to achieve the best esthetic outcome and to keep the preoperative vision, which was successfully accomplished. Lastly, although this treatment was successful considering the objectives and the follow-up carried out up to now, it is impossible to ensure at this moment that the dermoid could not eventually reappear despite the extensive technique used to guarantee a complete resection to avoid a possible recurrence.

Conclusions

ECCL is a rare disorder, but once detected, making an accurate diagnosis comprising both clinical and genetic aspects can facilitate the monitoring of possible complications, improve the multidisciplinary treatment, and offer valuable information for future therapy developments.

In our opinion, the surgical considerations taken into account for the treatment of this case may probably be extrapolated to the surgical treatment of high-grade dermoids similar to that of our patient, whether or not they are associated with ECCL.

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Conflict of interests

None.

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