Congenital Corneal Opacities Associated With Trisomy 8 Mosaicism Syndrome

Christopher Welsh, MD, Sina Khalili, MD,† Lili-Naz Hazrati, MD, PhD, FRCPC,‡ and Kamiar Mireskandari, FRCOphth, PhD†§*

Purpose: To describe the clinical, anterior segment optical coherence tomography (OCT) and histopathological features of 2 infants with congenital corneal opacities (CCOs) and undiagnosed trisomy 8 mosaicism syndrome (T8mS).

Methods: This is a retrospective case report documenting ocular and systemic findings, imaging, pathology and management of 2 patients with T8mS.

Results: An 11-month-old white male infant and a 4-week-old Asian female were initially seen for unilateral and bilateral CCOs, respectively. Corneal examination revealed para-axial anterior stromal opacities with blood vessels. Superficial irregular opacities were seen on OCT, and specular microscopy revealed normal endothelial cell morphology. One eye required superficial keratectomy to clear the visual axis and developed steroid-induced glaucoma in the early postoperative period, successfully treated with goniotomy. Both patients had hyperopia, anisometropia, and amblyopia, which was managed with glasses and patching. Cytogenetic testing (through microarray and fluorescence in situ hybridization) later diagnosed T8mS in both cases.

Conclusions: T8mS should be considered in the differential diagnosis for superficial CCOs with blood vessels. Anterior segment OCT can guide management and cytogenetics performed to confirm diagnosis. Systemic associations and, in particular, risk of acute myeloid leukemia and myelodysplastic syndromes warrant prompt diagnosis of this condition.

Key Words: pediatrics, cornea, corneal opacity, trisomy 8 mosaicism syndrome, optical coherence tomography

(*Cornea* 2018;37:1596–1600)

Trisomy 8 mosaicism syndrome (T8mS) is due to a somatic mutation in embryogenesis leading to a subset of cells having an extra chromosome 8. T8mS is characterized by a number of abnormalities that range from mental retardation, dysmorphic features (prominent forehead, domed occiput, broad nose with a flat bridge, low set prominent ears, dermatoglyphic patterns), and skin, musculoskeletal, hematological, urogenital, neurological, and cardiovascular clinical features.[1,2] Aside from strabismus, some of the rare reports of ophthalmologic findings include corneal opacities (typically unilateral), retinal dystrophy, optic nerve atrophy, optic disc coloboma, cataract, iris heterochromia, microphthalmos, ptosis, and pendular nystagmus.[3,4]

To our knowledge, this is the first report in the literature of 2 cases of congenital corneal opacity (CCO) with accompanying optical coherence tomography (OCT) imaging, specular microscopy, histology, and long-term outcomes including management with superficial keratectomy.

MATERIALS AND METHODS

We retrospectively reviewed 2 patients with CCOs who were subsequently diagnosed with T8mS. The data on clinical history, systemic and ocular findings, investigations, and treatments were recorded. Patients' guardians provided written consent for publication of personal information including medical record details and photographs.

CASE DESCRIPTION

Case 1

An 11-month-old white male with an unremarkable birth history was referred for evaluation of corneal opacity noticed in the left eye since birth. The medical history was significant only for cryptorchidism (underwent bilateral orchidopexy at 3 years old). Visual acuity was 0.2 and 0.3 Logarithm of the Minimum Angle of Resolution (logMAR) using Cardiff Cards (Cardiff University, Cardiff, United Kingdom) in the right and left eyes, respectively. Left corneal examination under anesthesia revealed superficial anterior stromal opacity at the superonasal region with blood vessels and a reticular pattern up to the visual axis (Fig. 1A). Corneal diameters were equal at 12 mm, and OCT of the cornea revealed a thickness of 546 μm including epithelial thickness of 59 μm and a 65-μm opacity in the anterior stroma in the left eye (555 μm corneal thickness with a 63-μm epithelial thickness in the right eye) (Fig. 1B). Cycloplegic refraction demonstrated +1.00 in the right and +4.00 in the left eye (with mild irregular astigmatism). All other aspects of the anterior segment and fundus examination were normal with no evidence of inflammation.

Received for publication June 30, 2018; accepted August 14, 2018. Published online ahead of print September 27, 2018.

From the *Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada; †Department of Ophthalmology and Vision Sciences, The Hospital for Sick Children, Toronto, Ontario, Canada; ‡Department of Pediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada; and §Department of Ophthalmology, University of Toronto, Toronto, Ontario, Canada.

The authors have no funding or conflicts of interest to disclose.

Correspondence: Kamiar Mireskandari, FRCOphth, PhD, Department of Ophthalmology and Vision Sciences, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada (e-mail: kamiar.mireskandari@sickkids.ca).

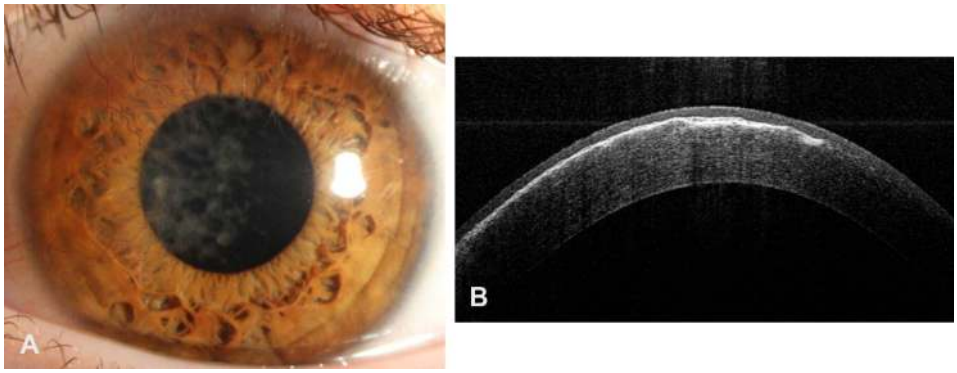

FIGURE 1. A, External photograph of the left eye showing anterior stromal opacity with blood vessels in the superonasal cornea. B, OCT of the cornea with thickness of 546 μm including epithelial and opacity thickness of 59 μm and 65 μm, respectively.

Cytogenetic testing using microarray and fluorescent in situ hybridization revealed trisomy 8 mosaicism (karyotype nuc ish(D8Z2 × 3[L2/200]arr(8) × 2-3) through peripheral blood sampling. Anisometropia and amblyopia were treated with glasses and patching as appropriate. At 5 years, visual acuity was 20/20 and 20/40 using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart in the right and left eyes, respectively. Corneal opacity remained unchanged, and the endothelial cell densities (ECD) were 3610 cells/mm^2 and 3460 cells/mm^2 in the right and left eyes, respectively.

Case 2

A 4-week-old Asian female child was referred for assessment of abnormal red reflexes. Her mother had a normal pregnancy and peripartum course with no history of sexually transmitted infections. She had bilateral reticular pattern anterior stromal opacities with vascularization involving the superonasal cornea up to the paraxial area in the right eye; however, the opacity covered the entire visual axis in the left eye (Fig. 2A–B). There were no epithelial defects, and corneal diameters were 9 mm. All other aspects of the anterior segment and fundus examination were normal. Notably, there was no keratitis or intraocular inflammation. Both eyes were responsive to light as appropriate for age. Anterior segment OCT measurements of corneal thicknesses were 530 μm and 522 μm with subepithelial opacity thicknesses of 100 μm and 103 μm in the right and left eyes, respectively (Fig. 2C). Keratometry readings were 44.12/50.87@101 and 43.75/50.00@79 using a handheld autorefractor in the right and left eyes, respectively.

Investigation demonstrated negative chlamydia, gonorrhea, herpes, and yeast cultures from the patient's eyes and maternal genitourinary swabs. Serology showed that the patient was cytomegalovirus IgG negative but rubella and herpes simplex virus IgGs positive as per her mother's immune status. She was managed with pupillary dilation using phenylephrine 2.5% to promote visual stimulation.

At 3 months old, left superficial keratectomy of 120 μm in the central 6 mm of the left cornea was performed using the Hessberg-Baron trephine (Barron Precision Instruments, Grand Blanc, MI). The postoperative regimen of tapering prednisolone acetate suspension (1%), moxifloxacin, atropine sulfate (0.5%), and dexamethasone ophthalmic suspension (0.1%) was initiated. The patient developed steroid response with rapid elevation of intraocular pressure (IOP) in the left eye (25–30 mm Hg), increase in the corneal diameter by 0.5 mm and disc cupping of 0.5 (0.1 in the right eye). The elevated left IOP was not fully controlled with maximal glaucoma medications and discontinuation of steroids, and therefore 180-degree nasal goniotomy was performed (9 months after superficial keratectomy). She did not require further glaucoma medications or surgery. Histopathologic analysis of the anterior lamellar keratoplasty corneal button showed variable epithelial thickness with focal pyknosis of basal cells and some regions appearing hydropic (Fig. 3). The Bowman layer was mostly lost with delicate elastic fibers in the areas of the deficient Bowman layer. Immunohistochemistry was negative for inflammatory and infectious etiologies. The patient was regularly followed up and managed with patching and glasses as appropriate.

At 5 years of age, her vision was 20/40 and 20/70 using the ETDRS chart wearing a prescription of +5.25 -2.25 ×25 and +7.00 -0.50 ×100 in the right and left eyes, respectively. Right corneal thickness was stable at 573 μm with para-axial opacity. The left eye also had stable thickness of 370 μm after superficial keratectomy, with a clear central axis (Fig. 1D–E). There was no sign of ectasia (final keratometric readings were 39.5/45.75@120 and 35.12/37.5@16 in the right and left eyes, respectively). All other examination parameters also remained stable after her glaucoma surgery. Her ECDs were 3436 cells/mm^2 and 1919 cells/mm^2; corneal diameters were 11.75 mm and 12.50 mm; IOPs were 20 mm Hg and 15 mm Hg; and cup to disc ratios 0.1 and 0.5 in the right and left eyes, respectively. The reduced ECD in the left eye was due to a larger corneal diameter and loss from glaucoma and its surgical intervention.[5]

The patient's systemic assessment revealed ankyloglossia (later requiring frenectomy for speech difficulty), pulmonary valve stenosis (resolved with age), low-set ears, mild frontal bossing, and abnormalities of hands and feet. No mental retardation or developmental concerns were detected. Karyotype analysis revealed trisomy 8 mosaicism (with karyotype Arr[hg19]8p23.3q24.3(158,0.48–146,295,771) × 2–3) with mosaicism proportion at 33% of cells.

DISCUSSION

This is the first report in the literature of T8mS CCOs with accompanying anterior segment OCT imaging and

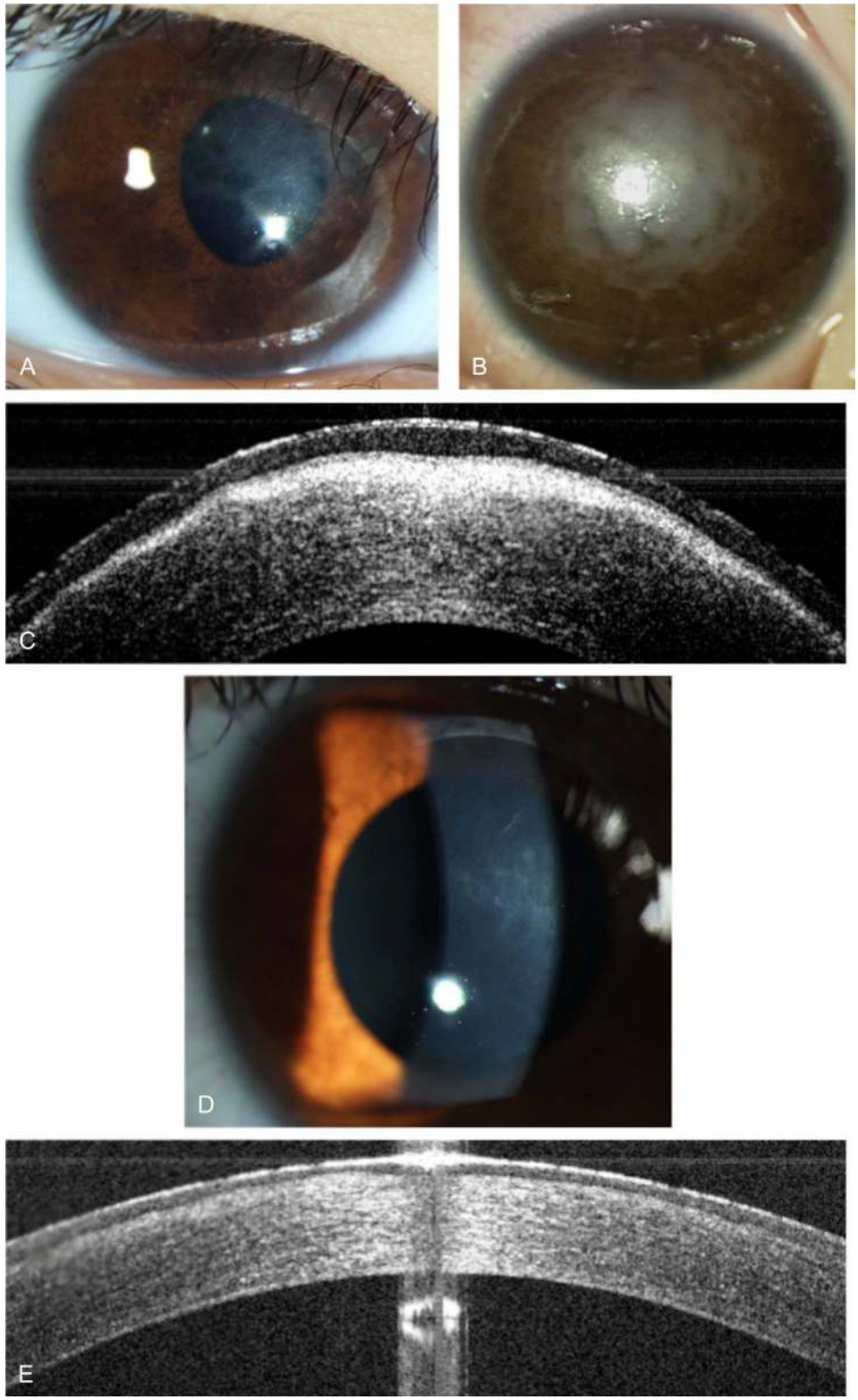

FIGURE 2. A and B, External photographs showing anterior stromal opacities with vascularization in the superonasal cornea up to the visual axis in the right eye and opacity covering the entire visual axis in the left eye. C, Preoperative OCT of the left eye showing corneal thickness of 522 μm with 103 μm subepithelial opacity. D, Postoperative photograph of the left eye after superficial keratectomy showing a clear central axis. E, Postsuperficial keratectomy OCT of the left eye showing no opacity and thickness of 370 μm.

long-term follow-up data of over 5 years. We present 2 patients: one with unilateral and the other with bilateral CCOs in the anterior stroma with vascularization.[2] T8 mS is an autosomal abnormality with a variable degree of phenotypic and cytogenic expression, often associated with a number of systemic and ophthalmic findings.[1–4] Individuals affected with mild T8mS may have a normal life expectancy, and the syndrome may go unrecognized into

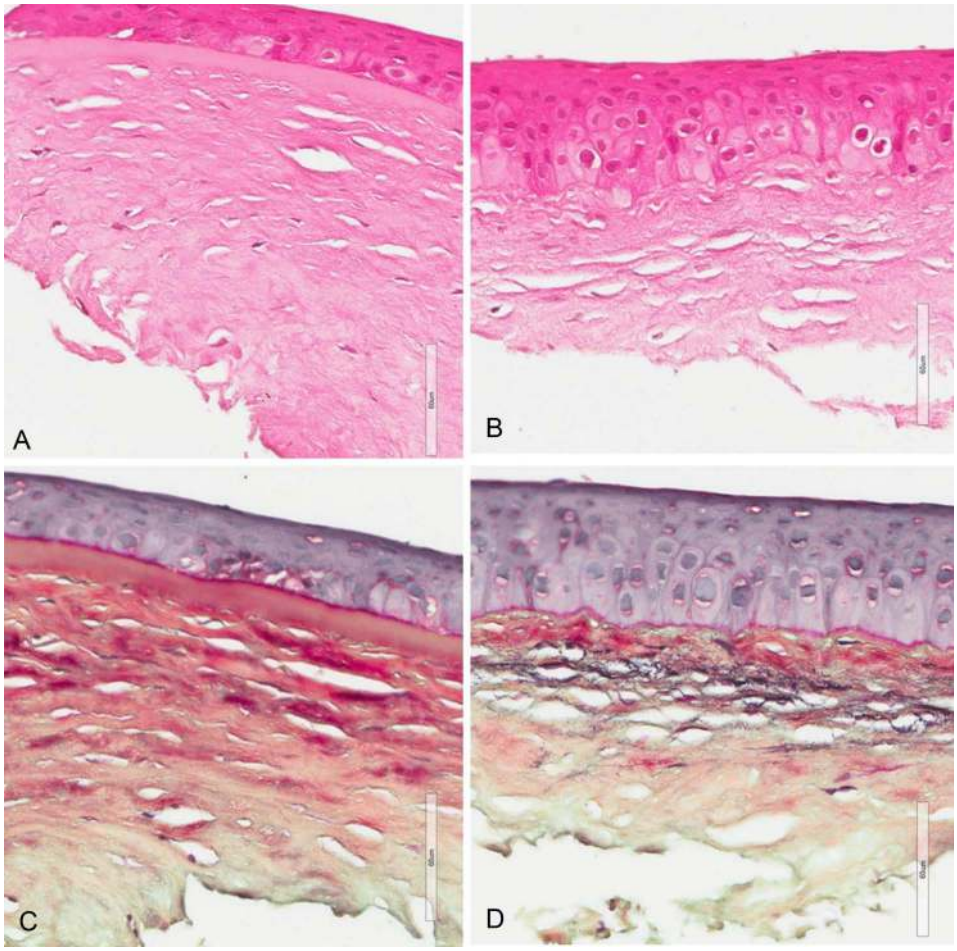

FIGURE 3. Photomicrographs of the left superficial keratectomy. A and B, Hematoxylin and eosin–stained peripheral (A) and central (B) areas of the cornea. A, The area of the peripheral cornea (clinically translucent) shows normal corneal histology with preserved Bowman layer and normal epithelium and stroma. B, In the central area of the cornea (clinically opaque), the Bowman layer is absent, and the overlying epithelium is pyknotic and edematous. C and D, Elastic trichrome stained peripheral (C) and central (D) cornea. C, Normal peripheral cornea. D, Elastic tissue is present in the area devoid of the Bowman layer. Scale bars represent 60 μm in (A–D).

adulthood.[6] Although parents were able to identify ophthalmic features in our patients, systemic and dysmorphic features were not obvious to parents or family physicians. Furthermore, patients with T8mS have an increased risk of neoplastic disorders, with 5% of patients with phenotypically normal T8mS developing myeloid malignancies (including acute myeloid leukemia and myelodysplastic syndrome).[7] Hence in these cases, the corneal changes were the only evident early manifestation of T8mS and can provide guidance for systemic/neoplastic work-up and pursuit of genetic testing.

T8mS should be considered in the differential diagnosis for superficial CCOs with blood vessels and cytogenetics arranged to confirm the diagnosis. Similarly, an ophthalmic examination should be requested by pediatricians in patients with T8mS to assess for corneal involvement, other associated congenital ocular abnormality, anisometropia, and amblyopia. In corneal involvement, an anterior segment OCT can guide management by delineating the depth of the opacity if superficial keratectomy is required. This surgical technique resulted in good vision with no recurrence in our patient and avoids long-term risks of penetrating keratoplasty. Although our case developed steroid-responsive glaucoma, it is not a typical feature of the disease and there is no associated goniodysgenesis or higher risk of glaucoma in patients with T8mS.

The pathogenesis of the CCOs is unclear; however, areas of trisomic cells may develop and undergo subsequent apoptosis, resulting in formation of a vascularized corneal scar secondary to an inflammatory response.[8] There are also alternative theories that believe that intrauterine infection and/or developmental abnormalities may contribute to CCOs.[9] However, our corneal tissue sample was negative for both inflammatory markers and infectious organisms. Our finding of a dense plaque appearance, richly vascularized fibrous tissue with overlying stratified squamous epithelium, and absent Bowman layer and basement membrane was consistent with previously reported histopathology.[9]

Our patients showed no progression of the CCO over 5 years, which indicates that there is no ongoing degenerative process involving the cornea and particularly the anterior stroma and Bowman layer. Furthermore, we demonstrate no recurrence of the opacity in our patient after lamellar keratectomy. Scott et al[9] demonstrated that an excised T8mS corneal lesion had 92% of cells trisomic for chromosome 8, compared with 44% in peripheral leukocytes. Given that there was no progression or recurrence of the lesion after removal, this further contributes to the CCO etiology being of developmental origin (rather than corneal dystrophy or infection). One limitation of our study is that the karyotype of the corneal cells remains unknown, but given the peripheral blood karyotype and clinical features, the

trisomic cells likely were the cause of the opacity. To date, limited genetic linkage data exist examining the contribution of aberrant chromosome 8 corneal gene expression (such as *EYA1* expression) to corneal opacities.[10] Further studies characterizing the genetic data of these trisomic corneal cells may aid in our understanding of the development of CCOs.

REFERENCES

1. Ismail S, Kamel AK, Eid MM, et al. Clinical and cytogenetic description of three patients with constitutional mosaic trisomy 8. *Middle East J Med Genet.* 2017;6:29–34.
2. Frangoulis M, Taylor D. Corneal opacities–a diagnostic feature of the trisomy 8 mosaic syndrome. *Br J Ophthalmol.* 1983;67:619–622.
3. Stone DU, Siatkowski RM. Congenital retinal dystrophy and corneal opacity in trisomy 8 mosaicism. *J AAPOS.* 2005;9:290–291.
4. Taban M, Marcotty A, Traboulsi EI. Optic disc coloboma and localized chorioretinal defects in constitutional partial trisomy 8 mosaicism. *Ophthalmic Genet.* 2006;27:103–105.
5. Elbaz U, Mireskandari K, Tehrani N, et al. Corneal endothelial cell density in children: normative data from birth to 5 Years old. *Am J Ophthalmol.* 2017;173:134–138.
6. Kurtyka ZE, Krzykwa B, Piatkowska E, et al. Trisomy 8 mosaicism syndrome: two cases demonstrating variability in phenotype. *Clin Pediatr.* 1988;27:557–564.
7. Paulsson K, Johansson B. Trisomy 8 as the sole chromosomal aberration in acute myeloid leukemia and myelodysplastic syndromes. *Pathol Biol.* 2007;55:37–48.
8. Stark D, Gilmore D, Vance J, et al. A corneal abnormality associated with trisomy 8 mosaicism syndrome. *Br J Ophthalmol.* 1987;71: 29–31.
9. Scott JA, Howard PJ, Smith PA, et al. Histopathology and molecular cytogenetics of a corneal opacity associated with the trisomy 8 mosaic syndrome (46, XY/47, XY,+ 8). *Cornea.* 1997;16:35–41.
10. Azuma N, Hirakiyama A, Inoue T, et al. Mutations of a human homologue of the Drosophila eyes absent gene (EYA1) detected in patients with congenital cataracts and ocular anterior segment anomalies. *Hum Mol Genet.* 2000;9:363–366.