Photo essay

Granular Corneal Dystrophy Type II

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Abstract

A paradigm shift has been observed in the classification of Granular corneal dystrophies (GCD). GCD is a bilateral, progressive, genetically determined and non-inflammatory disease limited to the cornea that has an autosomal dominant mode of inheritance. A 28 year old young male presented to us without any visual complaints. The examination of his cornea revealed the presence of diffuse linear, multiple round to granular, bread crumb like and stellate opacities extending from the sub-epithelium migrating down till the deep stroma, the classical clinical features of a heterozygous phenotypic variant of GCD type II.It progresses slowly and majority of the affected patients maintain a stable vision. Since this patient was asymptomatic therefore a complete ophthalmic examination in routine cases presenting to the oupatient clinics is indispensible. Various management options exist but a definitive treatment option is lacking.

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***Keywords:**. Granular Corneal Dystrophy Type II, Corneal Dystrophy.*

A paradigm shift has been observed in the classification of Granular corneal dystrophies (GCD) which can be attributed to the 2005 creation of The International Committee on the Classification of Corneal Dystrophies (Table 1 and 2).[1, 2, 3] GCD is a bilateral, progressive, genetically determined and non-inflammatory disease limited to the cornea that has an autosomal dominant mode of inheritance. Transforming growth factor beta-induced (TGFβI) gene located on chromosome 5q31 codes for keratoepithelin, a type of corneal stromal protein secreted by corneal epithelium. Recent research has suggested that excessive accumulation of the C-terminal of the mutant TGFB-I p (TGFB-I protein) as a result of mutation in this gene results in crystalloid accumulation in GCD corneas which plays a principal role in the pathobiology of GCD.[4 5] A 28 year old male tailor by occupation presented to us for his ophthalmic examination for applying for a driving license. He apparently had no visual complaints. On examination his unaided visual acuity (VA) in both eyes (BE) was 6/9. Bilateral cornea revealed the presence of diffuse linear, multiple round to granular, bread crumb like and stellate opacities extending from the sub-epithelium migrating down till the deep stroma (Figure 1 and 2). There was no significant refractive error on cycloplegic refraction, intraocular pressure was 12 and 14 mm Hg in the right eye and left eye respectively Bilateral fundus examination was unremarkable and so was the ocular examination in all other aspects. Although immunohistochemical testing to demonstrate a positive reaction with antibodies to microfibrillary protein, immunoglobulin G in the kappa and lambda light chains and light microscopy to stain hyaline and amyloid deposits with Masson trichome/Congo red was not performed nor was any genetic testing done on the patient, yet the clinical appearance was highly suggestive of a heterozygous phenotypic variant of GCD type II. GCD type II mostly starts in the second decade of life, visual acuity is rarely worse than 6/24 and these patients infrequently demonstrate recurrent corneal erosion (RCE) symptoms. The corneal opacities in heterozygous patient progress slow and majority maintain a stable VA.[6] Significant visual disabilities occur only later due to the natural history of

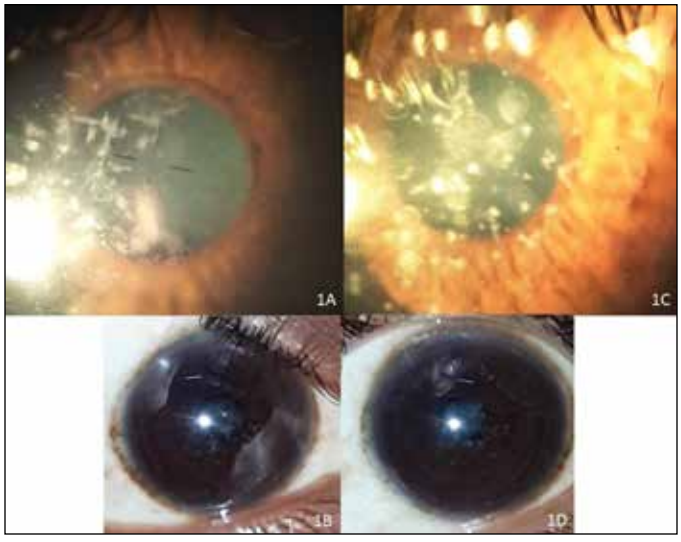

***Figure 1:** A-D: Slit lamp examination of the cornea of the right eye (Figure.1A) and the left eye (Figure.1C) reveal the presence of diffuse linear, multiple round to granular, bread crumb like and stellate opacities extending from the sub-epithelium migrating down till the deep stroma. Torch light examination of the right eye (Figure.1B) and the left eye (Figure.1D) show multiple dot like corneal opacities.*

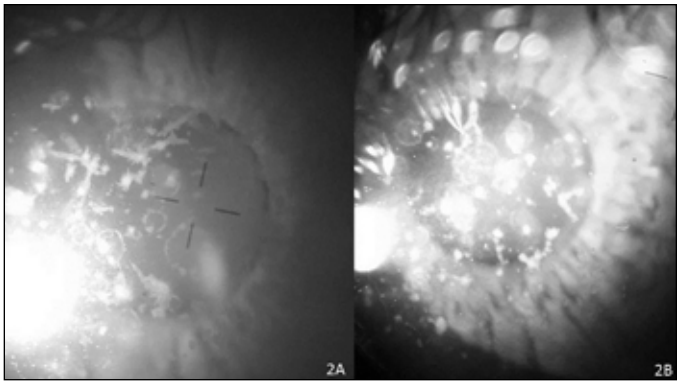

***Figure 2:** A-B: Rings or stellate-shaped snowflake stromal opacities between the superficial stroma and the mid stroma along-with lattice lines in deeper cornea are seen in the right eye on indirect retroillumination (2A) and also in the left eye (2B).*

Table 1: Descriptive categories developed by IC3D committee

Category	Description
C1	Gene has been mapped and identified and specific mutations are known.
C2	Dystrophy mapped to 1 or more specific chromosomal loci, but the gene(s) remains to be identified.
C3	The disorder has not yet been mapped to a chromosomal locus.
C4	A suspected new, or previously documented, corneal dystrophy, although the evidence supporting it being distinct, is not yet convincing.

the disease. Therefore our patient was instructed for a reexamination six months later and was educated on the possibility of development of RCE symptoms. GCD type II is observed globally now with a prevalence of 11.[5] affected persons per 10,000 population as per a Korean study and the term Avellino addressing this dystrophy is now obsolete. Broadly, GCD usually requires no treatment.1 Pressure patching, bandage contact lenses, artificial tear and hyperosmotic sodium chloride drops are first line options in RCE cases. Topical treatment in the form of steroids, immunomodulators, autologous serum and topical and oral macrolides are second line agents. Surgical intervention is the final treatment option that aims to reduce the frequency of RCE symptoms and improve VA. Anterior stromal puncture and phototherapeutic keratectomy provides a less invasive alternative to penetrating keratoplasty (PK) in GCD patients

Table 2: The IC3D classification and specific assays for various dystrophies

Type of dystrophy	Category	Specific assays
Epithelial and Subepithelial Dystrophies 1. Epithelial basement membrane dystrophy (EBMD)—majority degenerative	some C1	Maps (Sheets of intraepithelial, multilamellar, basal laminar material on Light microscopy {LM}). Dots – Cogan (Intraepithelial pseudocyst containing cytoplasmic debris on LM). Fingerprint lines (Rib-like intraepithelial extensions of basal laminar material on LM). Bleb (Irregular, subepithelial accumulation of fibrillogranular material on LM).
2. Epithelial recurrent erosion dystrophy (ERED) C4, (Smolandiensis variant) C3	C4; C3	Franceschetti corneal dystrophy (FRCD) - Alcian blue– positive deposits. Partial destruction and absence of the Bowman layer with intervening avascular connective tissue, pannus between the basal epithelium and Bowman layer. Negative Congo red staining. Keloid-like structure stains positive with Congo red indicating secondary amyloidosis in C3.
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3. Subepithelial mucinous corneal dystrophy (SMCD)	C4	Subepithelial band of eosinophilic, periodic acid–Schiff–positive, Alcian blue–positive, hyaluronidase-sensitive material is present anterior to Bowman layer.
4. Mutation in keratin genes: Meesmann corneal dystrophy (MECD)	C1	Intraepithelial cysts are seen filled with periodic acid–Schiff–positive cellular debris. The epithelium may be thickened and disorganized. Thickened multilaminar basement membrane with projections into the basal epithelium is observed. Stocker–Holt Variant The cornea in its entirety demonstrates fine, grayish punctate epithelial opacities that stain with fluorescein and fine linear opacities that may appear in a whorl pattern
5. Lisch epithelial corneal dystrophy (LECD)	C2	Diffuse cytoplasmic vacuolization of all cells in the affected area is seen. There is scattered staining on Ki67 immunohistochemistry
6. Gelatinous drop-like corneal dystrophy (GDLD)	C1	Subepithelial and stromal amyloid deposits are observed.
Bowman Layer Dystrophies 1. Reis–Bücklers corneal dystrophy (RBCD)—Granular corneal dystrophy type 3	C1	Bowman membrane is replaced by a sheet-like connective tissue layer with granular deposits that stain red with Masson trichrome.
2. Thiel–Behnke corneal dystrophy (TBCD) C1, potential variant	C2	Irregular thickening of the epithelial layer forming ridges and furrows of underlying stroma, with focal absences of epithelial basement membrane. Bowman layer is replaced by a fibrocellular layer between epithelium and stroma with a pathognomonic wavy saw-toothed pattern.

3. Grayson –Wilbrandt corneal dystrophy (GWCD)	C4	Characterized by variable patterns of opacification in the Bowman layer of the cornea which extend anteriorly into the epithelium with decreased to normal visual acuity.
Stromal Dystrophies 1. TGFBI corneal dystrophies A. Lattice corneal dystrophy a. Lattice corneal dystrophy, TGFBI type (LCD): Classic lattice corneal dystrophy (LCD1), variants (III, IIIA, I/IIIA, and IV) are C1 b. Lattice corneal dystrophy, gelsolin type (LCD2) (This is not a true corneal dystrophy but is included here for ease of differential diagnosis)	 C1 C1	Epithelial atrophy and disruption with degeneration of basal epithelial cells is seen with focal thinning or there is absence of Bowman layer that progressively increases with age. Eosinophilic layer is observed between epithelial basement membrane and Bowman layer; and stromal deposition of amyloid substance distorts the architecture of corneal lamellae.
B. Granular corneal dystrophy C1 i. Granular corneal dystrophy, type 1 (classic) (GCD1) ii. Granular corneal dystrophy, type 2 (granular-lattice) (GCD2) iii. Granular corneal dystrophy, type 3 (RBCD) = Reis–Bücklers	C1 C1 C1	GCD type 1- Multiple stromal deposits extend from deep epithelium to Descemet membrane. GCD type 2- Deposition of both typical deposits as observed in GCD1 along-with deposition of amyloid is seen on LM. Individual opacities stain with either Masson trichrome or Congo red. GCD type 3- There is an absence of the Bowman layer and a band of abnormal connective tissue is seen between the corneal epithelium and stroma but without the characteristic fuchsinophilic bodies.
2. Macular corneal dystrophy (MCD)	C1	Glycosaminoglycans (GAGs) accumulate intracellularly and extracellularly in the corneal stroma, corneal endothelium, and Descemet membrane (stain positively with Hale colloidal iron or Alcian blue). There are 3 variants of macular corneal dystrophy, based on the immunoreactivity of the macular deposits specific for the sulfated epitopes on antigenic keratan sulfate (AgKS): 1. Type I: No AgKS reactivity in the cornea or in the serum. 2. Type IA: Keratocytes manifest AgKS reactivity but the extracellular material does not. Serum lacks AgKS. 3. Type II: All the abnormal accumulations react positively with AgKS and the serum has normal or lower levels of AgKS.
3. Schnyder corneal dystrophy (SCD)	C1	Abnormal deposition of intra- and extracellular esterified and phospholipids and cholesterol is observed in basal epithelial cells
4. Congenital stromal corneal dystrophy (CSCD)	C1	The stromal lamellae are separated from each other in a regular manner.
5. Fleck corneal dystrophy (FCD)	C1	Swollen and vacuolated keratocytes are seen which contain GAG and complex lipids.
6. Posterior amorphous corneal dystrophy (PACD)	C3	Irregular stromal architecture is observed anterior to a thin Descemet membrane and focal attenuation of endothelial cells.
7. Central cloudy dystrophy of François (CCDF)	C4	Faint undulating appearance of the deep stroma and positive staining for GAGs is characteristic
8. Pre-Descemet corneal dystrophy (PDCD)	C4	Enlarged keratocytes are seen in the posterior stroma with vacuoles and intracytoplasmic inclusions containing lipid-like material
Descemet Membrane and Endothelial Dystrophies 1. Fuchs endothelial corneal dystrophy (FECD)	C1, C2, or C3	Diffuse thickening and lamination of Descemet membrane is seen. Sparse and atrophic endothelial cells, hyaline excrescences on thickened Descemet membrane called guttae is typical
2. Posterior polymorphous corneal dystrophy (PPCD)	C1 or C2	Descemet membrane with multiple layers of collagen on its posterior surface manifesting focal fusiform or nodular excrescences.
3. Congenital hereditary endothelial dystrophy 1 (CHED1)	C2	To date there is no convincing published evidence to support the existence of autosomal dominant (AD) CHED as a distinct entity and hence AD CHED, formerly known as CHED1 has been removed from the classification system.
4. Congenital hereditary endothelial dystrophy 2 (CHED2) – Autosomal recessive, now called CHED	C1	Diffuse thickening and lamination of Descemet membrane. Sparse and atrophic endothelial cells.
5. X-linked endothelial corneal dystrophy (XECD)	C2	Moon crater endothelial changes and subepithelial band keratopathy. Epithelium and Bowman lamella thinning. Anterior stroma with irregularly arranged collagen lamellae.Descemet membrane thickening with small excavations and pits. Loss of endothelial cells or atypical appearance.

to control RCE symptoms. Femtosecond Deep anterior lamellar keratoplasty (FDALK) and femtosecond laser-assisted keratoplasty (FLAK) enhance treatment outcomes.

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